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The Synthesis and Spectral Characteristics of Novel 7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiols

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Abstract

A variety of new 7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiols has been synthesized. The general synthetic route used for this purpose involves the condensation of substituted α,β-unsaturated ketones, 5-(4-substituted-benzylidene)-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-4-one with thiourea in the presence of sodium ethoxide. The structures of ring system obtained were investigated by MS, ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Pyrimidine, thiazole, α,β-unsaturated ketones, biological activities, pharmacophore.

Introduction

Pyrimidines are the most attractive objects, to synthesize novel fused heterocycles due to their structural diversity and significance in the development of broad range of therapeutics such as anti-cancer[1], anti-microbial[2], anti-tubercular[3], anti-malarial[4], anti-HIV[5], potential agent against congestive heart failure[6], selective type 4 phosphodiesterase[7], central nervous system activities[8], analgesic and anti-inflammatory agent[9]. The pyrimidine ring is also found in vitamins like thiamine**,** folic acid**,** and riboflavin etc. Recently, scientists' raised more attention regarding the synthesis of pyrimidine derivatives.

On the other hand 4-thiazolidinones play an essential role owing to their broad array of biological activities and industrial importance. The role of 4-thiazolidinone nucleus in the field of medicinal chemistry motivated us to keep on working on the synthesis of new derivatives having this moiety. They have biological activities mainly cox-2 inhibitors[10], inhibitors of bacterial enzyme, non nucleoside inhibitors of HIV Type 1 Reverse Transcriptase[11] (HIVRT). In present time 4-thiazolidones are recognized as an innovative group of anti-diabetic medicines and potent aldose reductase inhibitors, which acquire probability for the treatment of diabetes complications[12]. It has also been reported in literature that certain compounds bearing 4-thiazolidinone nucleus possess anti-microbial[13], anti-viral[14], anti-inflammatory[15], anti-cancer[16], anti-convulsant[17], anti-hyperglycemic activity[18].

It was conceited that if we link, these two active pharmacophores, together, we would achieve novel molecular templates exhibiting interesting biological properties. Combination of the thiazolidine moiety with the pyrimidine nucleus may enhance these activities. In sight of these previous conclusions, and in continuation of our awareness in the fictionalization of thiazolidine condensed pyrimidines, we report here in on the synthesis of a number of novel pyrimidine derivatives containing thiazolidine moiety.

To our knowledge, no attempt has been made in the literature to examine the feasibility of the preparation of the pyrimidines, addition on one side and substitution with substituted thiazolyl moiety on the other side on 4-thiazolidinones.

Methodology

Melting points were determined in open glass capillary and are uncorrected. Progress of reaction was monitored by using tlc on silica gel 'G' coated plates using benzene: methanol (9:1). IR spectra on KBr were recorded on FTIR-8400S, CE (SHIMADZU). Mass spectra were taken on 3000 LC/MS system. ^{1}HNMR spectra were recorded on model AC-300 F (Brucker) using $CDCl_3$/DMSO-d_6 as solvent. Chemical shift (δ) are given in ppm relative to signal for TMS as internal standard.

Synthetic aspect of compound 2-Chloro-N-(4-phenyl-thiazol-2-yl)-acetamide (2): Chloroacetyl chloride (0.02mole) was slowly added to a solution of 4-Phenyl-thiazol-2-ylamine **1a** (0.01 mole) in 20ml of dry benzene keep at 0-5^{0}C the reaction mixture was refluxed for 3 hrs and excess solvent removed under vacuum. The residue first wash with 5% solution of $NaHCO_3$ and then cold water. The crude product was recrystallized using ethanol to give cream color crystals of compound 3.

Synthetic aspect of compound 2-(4-Phenyl-thiazol-2-ylimino)-thiazolidin-4-one (3): A mixture of 2-Chloro-N-(4-phenyl-thiazol-2-yl)-acetamide (0.4g, 0.002 mol) and NH_4SCN (0.04g, 0.004 mol) were dissolved in 20ml of ethanol. This reaction mixture heated under reflux for 4 hrs. At the end point the reaction, mixture was cooled and poured on crushed ice. The crystals obtained were filter, wash, dry and recrystallize using ethanol.

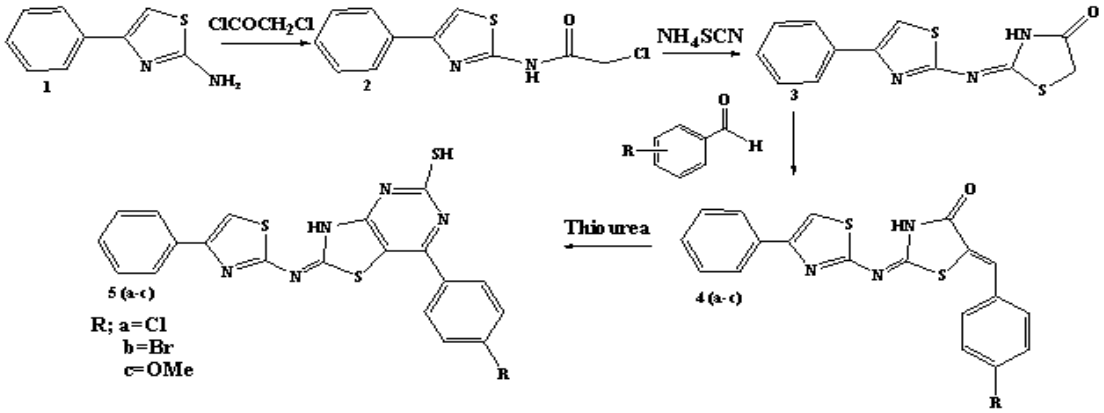
Synthetic aspect of compounds 5-(4-substituted-benzylidene)-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-4-one (4a-c): To a mixture of 2-(4-Phenyl-thiazol-2-ylimino)-thiazolidin-4-one (3) (0.4g, 0.001 mol) and various aromatic substituted aldehydes (0.001 mol) in ethanol (50 mL) cooled at 5-10^{0}C was added aqueous sodium hydroxide (70 %, 5mL) drop wise with constant stirring, then further stirred for 2h and left over night. This mixture was neutralized with concentrated hydrochloric acid, and then the solid separated was collected and crystallized using ethanol.

Synthetic aspect of compounds 7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiol (5a-c): To a mixture of 5-(4-substituted-benzylidene)-2-(4-phenyl-thiazol-2-ylimino)-thiazolidin-4-one 4a-c (0.5g, 0.001mol), thiourea (1.2g, 0.02mol) and sodium ethoxide (1.36g, 0.02mol) in 20ml ethanol were heated under reflux for 7-8 hrs. Solvent was withdrawn by distillation and obtained ppt. was reacted with glacial acetic acid (5ml) to dissolve sodium salt of the pyrimidine and refluxed for 15 min. then poured on crushed ice and solid obtained was recrystallize using ethanol to give compounds 5a-c.

Results and Discussion

This paper reports a simple and effective method to synthesize Pyrimidine derivatives. Our purpose was to synthesize a series of Pyrimidines derivatives through α,β-unsaturated ketones intermediates starting from substituted 2-amino thiazole. Preparation of the target compounds (5a-c) was initiated by the reactions of 4-Phenyl-thiazol-2-ylamine 1a with chloroacetyl chloride to afford the compound 2a. In IR spectrum of compound 2a, an absorption band at1700 cm-1 shows the presence of a carbonyl group. The ^{1}H- NMR spectrum (δ-ppm) of 2a showed one singlet at 4.27 ppm corresponding to the CH_2 group and a singlet at 8.00 due to NH proton of amide. ^{13}CNMR spectrum (δ-ppm) showed a characteristic singlet at 163.2 due to the carbonyl group. Cyclisation of 2a with NH_4SCN give the intermediate 4-thiazolidinone 3a in 85-93% yields. Their IR spectra revealed characteristic absorption band at the range of 1650 cm-1 shows the presence of carbonyl group of 4-thiazolidinone. Their 1H-NMR spectra (δ-ppm) revealed a singlet at 3.84 ppm assigned a CH_2 group in thiazolidinone ring. ^{13}CNMR spectrum (δ-ppm) showed a characteristic singlet at 35.7 corresponding to the methylene group. The intermediate 3a undergo reaction with substituted benzaldehydes to yield the corresponding α,β-unsaturated ketones 4a-c. The IR spectra of these compounds revealed beside the characteristic absorption bands corresponding to the carbonyl group. Their 1H-NMR spectra (δ-ppm) had a singlet at 7.42 ppm assigned to ethylene =CH proton of α,β-unsaturated ketone. Their ^{13}C-NMR spectra (δ-ppm) showed characteristic singlets at 120 to142 corresponding to the C=CH group of α,β-unsaturated ketones. Cyclocondensation of corresponding of α,β-unsaturated ketones with thiourea in presence of a base, the corresponding pyrimidine derivatives 5a-c were obtained in good yield. The IR spectra of these compounds revealed the characteristic absorption band at 1210 cm-1 due to C=N streaching of pyrimidine ring and a absorption band at 2578 cm-1 due to SH str. Their ^{1}H-NMR spectra (δ-ppm) had a singlet at 3.00 ppm assigned to one SH proton. ^{13}CNMR spectrum (δ-ppm) showed a characteristic singlet at 35.7 corresponding to the methylene group. Their 13C-NMR spectra (δ-ppm) showed characteristic singlets at 129.7, 153.5, 158.8 and 185.1 corresponding to the pyrimidine (scheme-1).

The synthesized pyrimidine derivatives (5a-c) were undergone physicochemical characterization and the obtained results are given in table-1. The formation of six-membered heterocycles were confirmed my their spectral data in which carbonyl stretching of the compounds 4a-c was disappeared in the resulting compounds 5a-c Similarly, the formation of the compounds was also established by the mass and NMR spectral data in table-2.



Scheme-1
Synthetic procedure of Pyrimidine

Table-1
Physicochemical characterization data for synthesized compounds 5a – 5c

S. No.	Compound Codes	Molecular Formula	M.W.	Yield (%)	M.P. (^oC)	Elemental Analysis Observed (Theoretical) percentage of C, H, N, and S			
						C	H	N	S
1.	5a	$C_{20}H_{12}ClN_5OS_3$	453.99	70	240^{o}C-242^{o}C	52.33 (52.91)	2.36 (2.66)	15.30 (15.43)	21.33 (21.19)
2.	5b	$C_{20}H_{12}BrN_5OS_3$	498.44	68	230^{o}C-232^{o}C	48.78 (48.19)	2.46 (2.43)	14.37 (14.05)	19.36 (19.30)
3.	5c	$C_{21}H_{15}N_5OS_3$	449.57	58	212^{o}C-214^{o}C	56.11 (56.10)	3.32 (3.36)	15.51 (15.58)	21.45 (21.40)

Table-2
Spectral data of synthesized compounds 5a – 5c

S. No.	Compound Codes	IR (KBr) cm-1	1HNMR ($CDCl_3$ / DMSO) δ ppm, ^{13}CNMR(DMSO)	m/z (% abundance)
1.	5a	3355 (N-H str.), 3045 (C-H str.), 2562 (S-H str.), 1586 (C=C str.), 1210 (C=N str.)	7.51-7.30 (9H, m, ArH), 8.23 (1H, s, ArH), 4.02 (1H, s, NH), 3.02 (1H, s, SH). ^{13}CNMR: δ=129.7,153.5,158.8,185.1(pyrimidine)	454 (74), 360 (100), 399 (34).
2.	5b	3354 (N-H str.), 3038 (C-H str.), 2578 (S-H str.), 1584 (C=C str.), 1210 (C=N str.).	7.79-7.48 (9H, m, ArH), 8.23 (1H, s, ArH), 4.02 (1H, s, NH), 3.00 (1H, s, SH). ^{13}CNMR: δ=116.2,156.5,158.8,169.1(pyrimidine)	498 (56), 415 (100), 351 (54).
3.	5c	3354 (N-H str.), 3037 (C-H str.), 2845 (OCH_3), 2560 (S-H str.), 1584 (C=C str.), 1350, 1230 (C=N str.).	7.90-7.87 (9H, m, ArH), 7.40 (1H, s, ArH), 4.00 (1H, s, NH), 3.73 (3H, s, CH_3), 3.00 (1H, s, SH). ^{13}CNMR: δ=158.1,161.9,162.2,169.1(pyrimidine)	450(25), 449(70), 355 (100).

7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiol (5a): Light yellow color solid, Yield: 66.4% m.p.:184-186^{o}C. 3420 (N-H str.), 3020 (C-H str.), 2560 S-H str.), 1560 (C=C str.), cm^{-1}; ^{1}H NMR(δ): 12.15 (1H, s, NH), 7.51-7.34 (9H, m, ArH), 7.60 (1H, s, ArH), 4.00 (1H, s, NH); MS:m/z 454(M^+ 74%), 360(100%), 399 (34%); Calcd (%) for $C_{20}H_{12}ClN_5OS_3$: C; 52.91, H; 2.66, N; 15.43, S; 21.19 Found: C; 52.33, H; 2.36, N; 15.30, S; 21.33; ^{13}CNMR: δ=129.7,153.5,158.8,185.1(pyrimidine).

7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiol (5b): Orange color solid, Yield: 68.8% m.p.:184-186^{o}C. 3422 (NH), 2930 (C-H str ArH), 2545 S-H str.), 1545 (C=Cstr ArH), 680 (C-S str); ^{1}H NMR(δ): 11.93 (1H, s, NH), 7.79-7.51 (9H, m, ArH), 7.45 (1H, s, ArH), 4.00 (1H, s, NH); MS:m/z 498(M^+ 56%), 415(100%), 351 (54%); Calcd (%) for $C_{20}H_{12}BrN_5OS_3$: C; 48.19, H; 2.43, N; 14.05, S; 19.30 Found: C; 48.78, H; 2.46, N; 14.37, S; 19.36; ^{13}CNMR: δ=116.2,156.5,158.8,169.1(pyrimidine).

7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2,3-dihydro-thiazolo[4,5-d]pyrimidine-5-thiol (5c): Light yellow color solid, Yield: 70.4% m.p.:184-186^{o}C. 3400 (NH), 2910 (C-H str ArH), 2555 S-H str.), 1545 (C=Cstr ArH), 680 (C-S str); ^{1}H NMR(δ): 10.82 (1H, s, NH), 7.79-7.51 (9H, m, ArH), 7.45 (1H, s, ArH), 4.00 (1H, s, NH);MS:m/z 449(M^+ 70%), 450(65%), 355(100%); Calcd (%) for $C_{21}H_{15}N_5OS_3$: C; 56.10, H; 3.36, N; 15.58, S; 21.40 Found: C; 56.11, H; 3.32, N; 15.51, S; 21.45; ^{13}CNMR: δ=158.1,161.9,162.2,169.1(pyrimidine).

Conclusion

In summary, we have established the formation of 7-(4-substituted-phenyl)-2-(4-phenyl-thiazol-2-ylimino)-2, 3-dihydro- thiazolo [4,5-d]pyrimidine-5-thiols by the reaction of α,β-unsaturated ketones and thiourea. This method can apply to synthesize a large number of such derivatives having pharmacological significance.

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