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Spectroscopic Identification and Synthesis of Derivatives of Pyrimidine 2- Thione Via Two Different Spacers

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Abstract: A new series of pyrimidine -2-thione derivatives were synthesized via two routes and designated as antifolate. The heterocyclic ring was prepared by direct reaction of benzoyl acetone with thiosemicarbiazide in acidic medium. Also, the pyrimidine-2-thione ring reacts with p-aminobenzoic acid to form 4-amino-N-(4-methyl-6-phenyl)-2-thioxypyrimidine 1[2H] –yl benzamide. The second route synthesis 5-[{4-methyl-6-phenyl-2-thioxo pyridine-1-yl amino}-4-(4-methyl phenylsulfonamido)-5-oxobenzoyl] pentanoic acid. All structures were elucidate by their physical & spectroscopic data FTIR, ^{1}H &^{13}C NMR.

Keywords: Antifolate, P-aminobenzoic Acid, Pyrimidine, NMR

1. Introduction

In recent years, 5- substituted pyrimidine-2-thione derivatives have drawn great attention for their anti cancer activity by inhibiting DNA synthesis. [1, 2].

Pyrimidine and their derivatives have been found to possess a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, analgesic, antiviral and anticancer activities [3]. Nitrogen containing heterocyclic ring such as pyrimidine is a promising structural moiety for drug design. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological and therapeutically activities [4, 5].

The aim of this study was designated to synthesis of pyrimidine -2-thione derivatives via two different spacers as expected as antifolate agent.

2. Experimental

2.1. Chemicals

All reagents were purchased from commercial sources and used without further purification, the employed chemicals and there supplier from BDH &Fluka companies.

2.2. General

All melting points were uncorrected and determined by the Electro-thermal IA 9100 melting point apparatus. All reactions were monitored by TLC using pre-coated Aluminum sheet silica gel Merck 60 F 254 and were visualized by iodine vapourand detected the spots using UV lamp and purification using micro column with silica gel. The infra-red (IR) spectra were recorded using potassium bromide disc technique on Bruker optics Co.; Alpha P, IR Spectrophotometer. The proton nuclear magnetic resonance (^{1}H NMR) & Carbon -13 nuclear resonance (^{13}C NMR) spectra were performed on Bruker 400MHz Spectrophotometer using tetramethylsilane (TMS) as internal standard. Chemical shift values (δ) are given using parts per million scale (ppm) in UK. Chemical naming, calculation of molecular weight (M. wt) of new compounds were performed by Chem Draw 12 software.

2.3. Route A

2.3.1. 1-Amino-4-Methyl–6–Phenyl Pyrimidine 2-Thione [6]

Mix 0.01 mole of benzoyl acetone with 0.01 mole

thiosmicarbizide in 50 ml of absolute ethanol, add 3 drops of pyridine then reflux for 5h, then concentrated the solvent until yellow precipitate was formed. Crystallization from absolute ethanol with 95% yield, m. p. (160-162); Reported m. p, (160-162). [6].

2.3.2. 4-Amino N-(4-Methyl-6 Phenyl)-2-Thioxy Pyrimidin 1-yl-Benzamide (Peptide Bond Formation) [7]

A 0.005 mole of 4-acetylaminobenzoic acid was dissolved in 10 ml of CH_2Cl_2, followed by addition of 0.005 mole of 1-amino-4-methyl-6-phenyl pyrimidine-2–thione which was already dissolve in 7 ml of CH_2Cl_2. The mixture was chilled (-10ºC), then add the solution of (0.006 mole, 1.24g of DCC in 10 ml of CH_2Cl_2) with stirring for 3h at 0ºC, then complete stirring for 24h at r.t, filter the DCU by product ignored. The filtrate was evaporated under reduce pressure. The red oily product can be solidified in ethyl acetate. The crud product was treated twice with 5% acetic acid and repeated twice with 5% sodium bicarbonate solution. The ethyl acetate extract was dried with Magnesium sulfate anhydrous, filter then evaporate under reduce pressure. Recrystallization using a mixture of ethyl acetate and petroleum spirit (60-80ºC). The percentage yield=83%, m. p=195-194ºC.

2.3.3. Protection of N-Acetyl 4-Amino Benzoate Derivative [8]

Mix 0.5g of 4-amino N-(4-methyl-6-phenyl)-2-thioxy pyrimidin 1 [2H] yl-benzamide with 2mL of 70% H_2SO_4 and reflux for 30min. The solution was cooled and pour into ice. The precipitate was crystallized with abs. ethanol to get yellow fine crystal. The percentage yield=88%; m. p=211-213ºC.

2.3.4. N2-Acetyl-N1-[4-{4-Methyl-6-Pheny-2 Thioxy Pyrimidine 1-yl Amino Carbonyl} Phenyl]-ª-Glutami [7]

A 0.001 mole of 4-amino-N-(4-methyl-6-pheny-2-thioxy pyrimidin 1-yl) benzamide was mixed with 0.001 mole of N-acetyl L-glutamic acid in 50 ml of CH_2Cl_2 using the procedure of peptide bond synthesis. The percentage yield 65%; m. p=142-144ºC.

2.4. Route B

2.4.1. 4-[{(4-Methylphenyl) Sulfonyl} Amino] Benzoic Acid [9] 2.4.1

A 0.01 mole of PABA was mixed with 0.01 mole of p-toluoyl sulfonyl chloride in 25 mL pyridine as solvent. Reflux the mixture for 30 min, then pour into 25mL of 5% HCL with stirring until complete the reaction. The white powder was crystallized with mixture of ethanol- water. The percentage yield= 90%, m. p=196-199ºC.

2.4.2. Diethyl–N-[4{4-(Methylphenyl) Sulfonyl} Amino] Benzoyl Glutamic Acid [7]

Mix 1: 1 mole of 4-[{(4-methylphenyl) sulfonyl} amino] benzoic acid with Diethyl L-glutamate in 30ml of CH_2Cl_2 using DCC. Then, follow the same procedure of peptide bond formation. The product was hydrolyzed using 10% NaOH solution. The white precipitate with percentage yield=84%, m. p. =124-126ºC.

2.4.3. 5-[{4-Methyl-6-Phenyl-2-Thioxo Pyridine-1-yl Amino}-4-(4-Methyl Phenylsulfonamido)-5-Oxobenzoyl] Pentanoic Acid [7]

A 0.003 mole of Diethyl –N-[4{4-(methylphenyl) sulfonyl} amino] benzoyl glutamic acid with 0.003 mole of 1-amino-4-methyl-6-phenyl pyrimidine-2-thione in 25 ML CH_2Cl_2 using DCC and follow the same procedure in peptide bond formation. The percentage yield=63%, m. p=(152-154ºC).

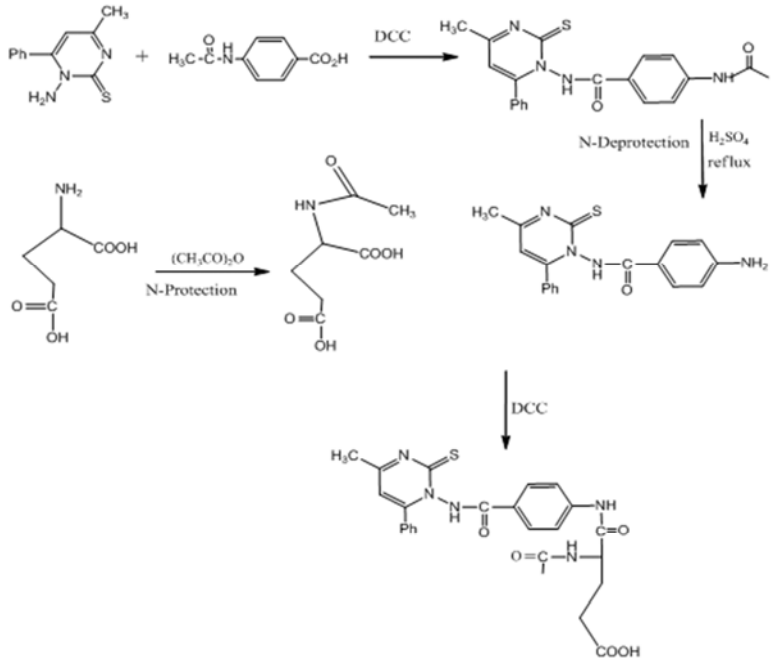


Figure 1. *Route –A of synthesis of pyrimidine derivatives.*

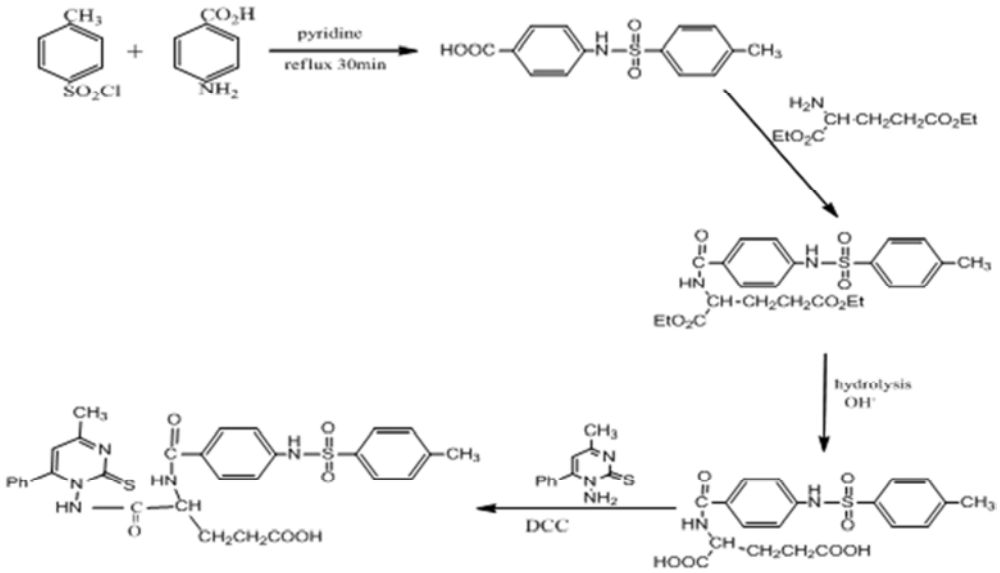
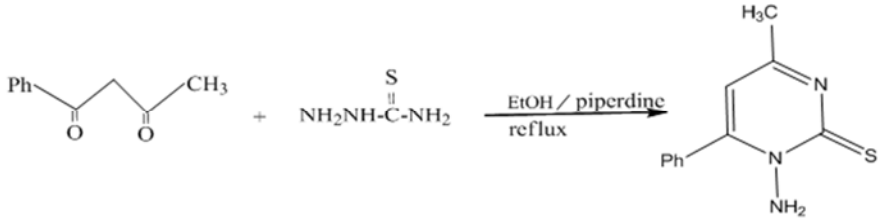


Figure 2. *Route –B synthesis of 5-[{4-methyl-6-phenyl-2-thioxo pyridine-1-yl amino}-4-(4-methyl phenylsulfonamido)-5- oxobenzoyl] pentanoic acid.*

3. Results& Discussion

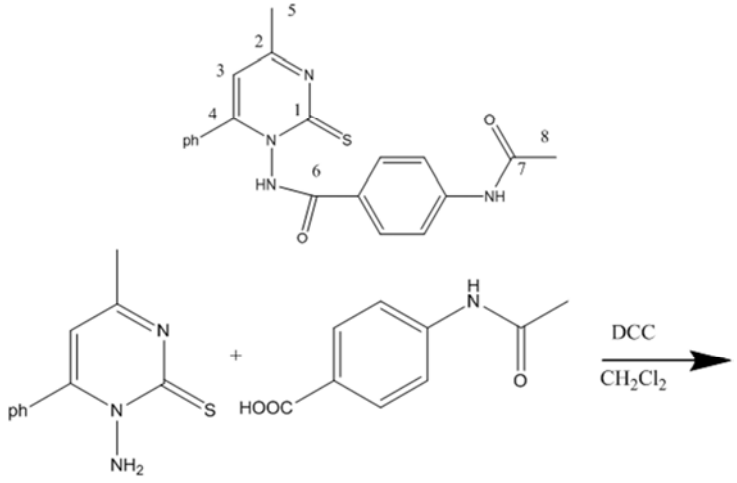
3.1. Route A

Pyrimidine and their derivatives are biologically very important heterocyclic agents to be antagonist of folic acid. This study was designated to prepare anti-folate via pyrimidine 2-thione ring as a nucleus and can be tested against different types of disease. Some new pyrimidine derivatives were synthesized via two different spacers in good yields in (Schemes 1&2), The sequence of the reaction followed in the synthesizes of the target compounds. The structures of the later products were assigned on the basis of their physical and spectral data. [6].



Two routes of synthesis new pyrimidine derivatives (scheme 1), route A was discussed the pyrimidine

ring formed via the reaction of benzoyl acetone with thiosemicarbazide in pyridine as catalyst with heat and cyclization will takes place via 1,4 Michael addition to form 1-amino4- methyl-6-phenyl pyrimidine-2-thione.IR spectra show the following characteristic bands: υ_{cm-1}:3216 (NH_2) 3085(CH) for aromatic, while 2997&2842 for (CH)symmetrical and asymmetrical bands. The C=N was appeared at 1593 & 1158 for (C=S). [10].



The IR spectra of the reaction products showed in each compound three or four characteristic functional groups corresponding 2 (NH) functional groups in the regions (3234, 3261) cm^{-1}, while the CH of aromatic (3153) cm $^{-1}$and aliphatic stretching ranges are (2930, 2885) cm^{-1}, in addition to a carbonyl absorption band s assigned C=O & C=N for (1716 & 1684) cm^{-1}, as well as other characteristic bands (C=N) 1508 cm^{-1} & (C=S) at 1182 cm $^{-1}$. ^{1}H & ^{13}C NMR spectrum of the final products are assigned are listed in Table 1. [7].

Table 1. *^{1}H & ^{13}C NMR of 4-Amino N-(4-methyl -6-phenyl)-2-thioxy pyrimidin 1-yl-benzamide.*

Position	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
1	-	176.18 C=S
2	-	170.43 C=N
3	6.48 (s, 1H) pyrimidine	113.19 CH (Pyrimidine)
4	7.30-7.43 (m,5H) ph	162.90 C=(Pyrimidine)
5	3.06 (s, 3H) CH_3	23.79 CH_3
6	7.76- 8.02 (dd, 4H) ph	164.92 C=O
7	7.24 (br, 1H) NH	166.63 C=O
8	2.23 (s,3H) CH_3	24.83 CH_3
	6.48 (s, 1H) NH	-

IR spectra data show the following characteristic for N^{2}-acetyl-N^{1}[4-{4-methyl-6-phenyl-2-thioxy pyrimidin-1 (2H)–yl amino carbonyl} phenyl]–α-glutamine peaks υ $_{cm-1}$: 3285, 3242 (NH), 3248 (OH), 3248 (CH) aromatic, 2926.2850 (CH) aliphatic, 1761 (COO), 1670,1653,1639 (C-NCO) amide, 1512 (C=C), 1182 (C=S). The nmr investigation are listed in Table 2. This novel structure was resemble to the folic acid derivative with three parts, L-glutamic acid, p-aminobenzoic acid and substituted pyrimidine ring.

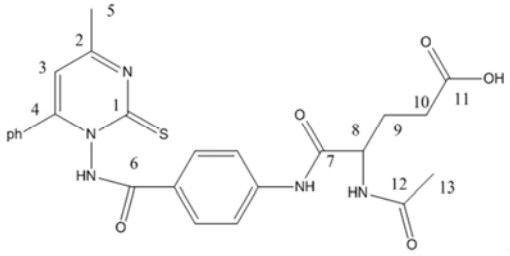


Table 2. *^{1}H & ^{13}C NMR of N^{2}-acetyl-N^{1} [4-{4-methyl-6-phenyl-2-thioxy pyrimidin-1 (2H)–yl amino carbonyl} phenyl]–α-glutamine.*

Position	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
1	-	177.46 C=S
2	-	172.56 C=N (Pyrimidine)
3	6.59 (s, 1H) pyrimidine ring	112.00 CH (Pyrimidine)
4	-	161.57 CH-N (Pyrimidine)
5	2.31 (s, 3H) CH_3	22.74 CH_3
6	-	161.76 C=O
7	7.21 (br, 1H) NH	170.35 C=O
8	4.61 (t, 1H) CH	51.54 CH
9	2.24 (q, 2H) CH_2	27.40 CH_2
10	3.13 (t, 2H) CH_2	30.57 CH_2CO
11	9.95 (s, 1H) OH	176.74 C=O
12	-	165.13 C=O
13	2.09 (s,3H) CH_3	25.15 CH_3
Others		120.99-142.33 Two ph (rings)

3.2. Route B

The second route of reaction between Toulyol sulfonyl chloride and p-aminobenzoic acid in pyridine to form 4 [{(4-methylphenyl) sulfonyl} amino] benzoic acid, this route was coupled the sulfonyl linker (spacer) with amino group of p-amino benzoic acid, the IR spectra υ $_{cm-1}$ show the following peaks: 3375 (OH), 3236 (NH), 3052 (CH)aromatic, 2946, 2851 (CH)aliphatic, 1700 (C=O), 1506 (C=C), 1083 (S=O) sulfonamide (scheme 2).

Another intermediate diethyl N-[4-{4-(methyl phenyl) sulfonyl} amino] benzoyl glutamate was formed via the reaction of 4 [{(4-methylphenyl) sulfonyl} amino] benzoic acid and diethyl glutamate. IR spectra shows the following characteristic bands υ_{cm-1}: 3232 (NH), 3088 (CH) aromatic, 2855 (CH) aliphatic, 1715 (C=O) ester, 1684 (CONH) amide, 1078 (S=O). While proton and C-13 NMR values are listed in Table 3.

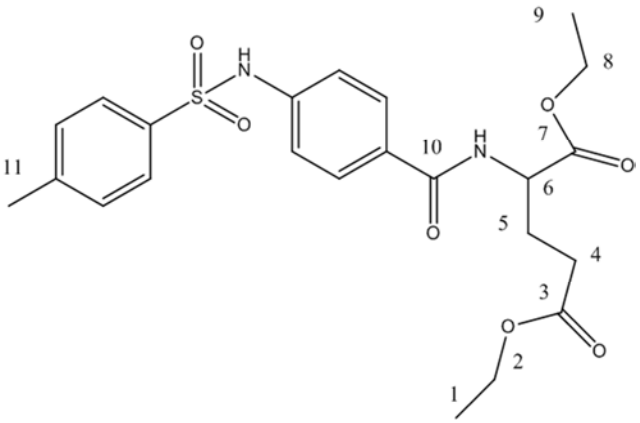


Table 3. *^{1}H & ^{13}C of diethyl N-[4-{4-(methyl phenyl) sulfonyl} amino] benzoyl glutamate.*

Position	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
1	1.36 (t,3H) CH_3	14.69
2	4.17 (q,2H) CH_2	51.79
3`	-	174.30 (C=O)
4	2.41 (t, 2H) CH_2	30.79
5	2.28 (m,2H) CH_2	25.45
6	5.83 (m, 1H) CH	53.56
7	-	173.12 (C=O)
8	5.52 (q,2H) CH_2	61.17
9	1.36 (t,3H) CH_3	14.69
10	-	168.01 (C=O)
11	2.37 (s,3H) CH_3	21.30
NH	4.31 (br, 1H) NH	-
Aromatic	7.39-7,73 (dd, 8H) two phenyl rings	126.13-142.22 multiple peaks

Finally, the 5-[{4-methyl-6-phenyl-2-thioxo pyridine-1-yl amino}-4-(4-methyl phenylsulfonamido)-5 oxobenzoyl] pentanoic acid was synthesized in Route –B. IR spectra shows the following characteristic bands υ_{cm-1}: 3378 (OH), 3254, 3220, 3146 three NH bands, 3044 (CH) aromatic, 2957&2922 (CH) aliphatic, 1716 (C=O) for carboxylic acid moiety, 1635&1622 (CONH) amide, 1508 (C=C), 1170 (C=S), 1073 (S=O). The nmr data are listed in Table 4, Further biological activities s was needed as antimicrobial or antifolate activities.

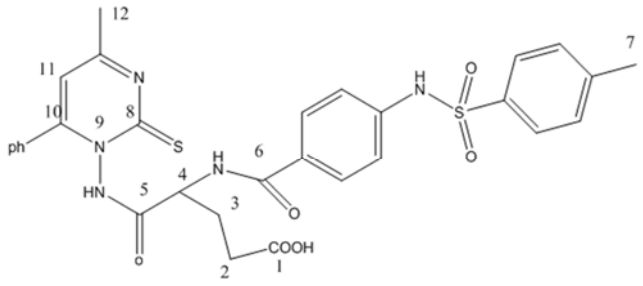


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Table 4. *^{1}H & ^{13}C-NMR of 5-[{4-methyl-6-phenyl-2-thioxo pyridine-1-yl amino}-4-(4-methyl phenylsulfonamido)-5- oxobenzoyl] pentanoic acid.*

Position	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
1	-	181.68 C=O
2	2.20 (t, 3H) CH_2	30.57
3	2.09 (m,2H) CH_2	27.30
4	4.66 (m, 1H) CH	54.02
5	-	176.74 C=O
6	-	169.01 C=O
7	2.36 (s, 3H) CH_3	26.51
8	-	180.49 C=S
9	-	167.40 CH Pyrimidine ring
10	-	126.44 CH pyrimidine ring
11	6.54 (s,1H) CH pyrimidine ring	141.60 CH pyrimidine ring
12	2.46 (s,3H) CH_3	21.12
	7.85 (BR, 1H) NHCO	-
	7.21- 7.39 (m, 13H) three phenyl rings	127.68-145.10 phenyl rings

4. Conclusion

The pyrimidine-2-thione derivatives prepared by direct coupling either by p-aminobenzoic acid or sulfonyl spacer with pyrimidine nucleus as antifolate. The products were identified using FTIR and ^{1}H & ^{13}C NMR spectroscopic analysis.

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