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Studies on Synthesis of Pyrimidine Derivatives and their Pharmacological Evaluation

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Abstract: 1,3,4-oxadiazoles were associated with broad spectrum of biological activities including antituberculosis, anticonvulsant, anti-inflammatory, insecticidal, antifungal, analgesic and antitumor properties. Morpholine derivatives find their wide spectrum of antimicrobial activity and exhibit anthelmintic, bactericidal and insecticidal activity. Pyrimidine derivatives are also reported to possess antibacterial, antimicrobial, antifungal, anticancer and anticonvulsant activities. Encouraged by this observations we decided to synthesised novel pyrimidine derivatives.

Keywords: Oxadiazoles, Pyrimidine Derivatives, Synthesis

Introduction

The biological significance of the pyrimidine derivatives has led us to the synthesis of substituted pyrimidine. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities.¹ The synthesis of substituted pyrimidine and many detailed reviews have been appeared.^{2,3}

The nitrogen containing fragment may be an amidine, urea, thiourea or guanidine and acetyl acetone serves as an excellent illustrative example in that it readily undergoes reaction with formamidine,⁴ guanidin,⁵ urea,⁶ or thiourea⁷ to produce the corresponding 4,6-dimethyl pyrimidine.

Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. Pyrimidine derivatives possess several interesting biological

activities such as antimicrobial⁸, antitumour⁹ and antifungal activities¹⁰. Many Pyrimidine derivatives are used for thyroid drugs and leukemia.

Step – 1

2-Morpholino-3-pyridinyl acid hydrazide

2-{2-(Morpholino)-3-pyridinyl}-5-mercapto-1,3,4-oxadiazole : (A)

Step – 2

Step – 3

Step – 4

Step – 5

Where R =	(TN-1 to TN-10)	
	4- CH ₃ ·C ₆ H ₄	- TN-1
	4-N(CH ₃) ₂ ·C ₆ H ₄	- TN-2
	2-OH·C ₆ H ₄	- TN -3
	4-OH·C ₆ H ₄	- TN -4
	4-Cl·C ₆ H ₄	- TN -5
	2,4-(Cl) ₂ ·C ₆ H ₃	- TN -6
	4-F·C ₆ H ₄	- TN -7
	2-OCH ₃ ·C ₆ H ₄	- TN -8
	4-OCH ₃ ·C ₆ H ₄	- TN -9
	3,4,5-(OCH ₃) ₃ ·C ₆ H ₂	- TN -10

Experimental

Step-1: Preparation of 2-{2-(Morpholino)-3-pyridinyl}-5-mercapto-1,3,4-oxadiazole (A)

To a solution of 2-Morpholino-3-pyridinyl acid-hydrazide (0.1 mole, 22.2 g.), CS₂ (0.1 mole, 7.6 ml) and 20% KOH solution (10 ml) in methanol (82 ml) was added and refluxed for eight hours. After the completion of reaction, the resultant mixture was poured in crushed ice. Product was filtered, washed with water and crystallized from ethanol to give white needles of the title compound.

Step-2: preparation of 1-(2,4-dichloro-5-fluoro phenyl)-3(aryl)-2-propene-1-one (e)

To a thoroughly stirred solution of 2,4-dichloro-5-fluoro acetophenone (0.05 mole, 9.7 g.) & aromatic aldehyde (0.05 mole, 5.3 g.) in methanol (98 ml.), was added 20% NaOH solution (10 ml.). The reaction mixture was stirred for thirty minutes at room temperature and left over night. After the completion of reaction, it was poured into ice water, acidified to neutral, filtered and crystallized from ethanol.

Step-3: preparation of 2-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidine: (f)

A mixture of (E) (0.05 mole, 15.3 g.), guanidine nitrate (0.15 mole, 18.3 g.) and sodium methoxide (25%) in methanol (100 ml.) was refluxed for six hours. After the completion of reaction, the resultant mixture was cooled to room temperature. Separated product was filtered, washed with water, dried and crystallized from methanol.

Step-4: preparation of n-chloro acetyl- 2-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidine (g)

In benzene (30 ml), chloro acetyl chloride (0.05 mole, 5.6 ml) and 2-3 drops of TEA were added and the mixture was stirred in water bath for 10 mins. The solution of (F) (0.05 mole) in benzene (80 ml) was added drop wise and refluxed for two hours. Then cooled the reaction mixture. The resulting white precipitates were filtered and washed with benzene, purified by recrystallization from alcohol.

Step-5: preparation of 2-[[2-(morpholino)-3-pyridinyl-5-thio]-2-oxoethyl oxadiazolyl]-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidine:

To a solution of (D) (0.005 mole) in acetone, (G) (0.005 mole) and KOH solution (10 ml) in acetone (80 ml) was added and refluxed for two hours. After the completion of reaction, the resultant mixture was poured in to crushed ice. Product was filtered, washed with water and crystallized from ethanol.

Similarly other compounds (TN-2) to (TN-10) were prepared by the above method from intermediate (D) and the corresponding N-chloro acetyl-2-amino-4-(2,4-dichloro-5-fluoro)-6-(aryl)-pyrimidines (G) and were purified by crystallization from absolute alcohol.

Table . 1 2-[[2-(morpholino)-3-pyridinyl-5-thio]-2-oxoethyl oxadiazolyl]-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidines (TN-1 to TN-10)

S.No	R	Mol. Formula	M.P. °C	Yield %	Elemental Analyses %		
					C	H	N
TN-1	4-CH ₃ C ₆ H ₄	C ₃₀ H ₂₄ N ₇ O ₃ SFCl ₂	182	75	R 55.22	3.71	15.07
					F 55.18	3.62	14.99
TN-2	4-N(CH ₃) ₂ C ₆ H ₄	C ₃₁ H ₂₇ N ₈ O ₃ SFCl ₂	162	60	R 54.63	3.99	16.44
					F 54.59	3.84	16.18
TN-3	2-OH C ₆ H ₄	C ₂₉ H ₂₂ N ₇ O ₄ SFCl ₂	155-157	60	R 53.22	3.39	14.98
					F 53.17	3.32	14.93
TN-4	4-OH C ₆ H ₄	C ₂₉ H ₂₂ N ₇ O ₄ SFCl ₂	175	68	R 53.22	3.39	14.98
					F 53.16	3.31	14.89
TN-5	4-Cl C ₆ H ₄	C ₂₉ H ₂₁ N ₇ O ₃ SFCl ₃	195	70	R 51.76	3.15	14.57
					F 51.71	3.09	14.51
TN-6	2,4-(Cl) ₂ C ₆ H ₃	C ₂₉ H ₂₀ N ₇ O ₃ SFCl ₄	205-206	73	R 49.26	2.85	13.86
					F 49.20	2.78	13.81
TN-7	4-F C ₆ H ₄	C ₂₉ H ₂₁ N ₇ O ₃ SF ₂ Cl	178	70	R 53.09	3.23	14.94
					F 53.02	3.15	14.86
TN-8	2-OCH ₃ C ₆ H ₄	C ₃₀ H ₂₄ N ₇ O ₄ SFCl ₂	152	62	R 53.90	3.62	14.67
					F 53.85	3.52	14.61
TN-9	4- OCH ₃ C ₆ H ₄	C ₃₀ H ₂₄ N ₇ O ₄ SFCl ₂	178	65	R 53.90	3.62	14.67
					F 53.82	3.51	14.61
TN-10	3,4,5-(OCH ₃) ₃ C ₆ H ₂	C ₃₂ H ₂₈ N ₇ O ₆ SFCl ₂	215	78	R 52.75	3.87	13.46
					F 52.69	3.81	13.39

IR Spectral Data

(TN-15)

IR (KBr):	1265 cm^{-1}	(-C-O- stretching in oxadiazole)
	1545 cm^{-1}	(-C=N- stretching in oxadiazole)
	1680 cm^{-1}	(>C=O- stretching in amide)
	1568 cm^{-1}	(-NH- deformation in amide)
	3248 cm^{-1}	(-NH stretching in amide)
	1245 cm^{-1}	(-C-O-C- stretching (asym.) in alkanyl ether)
	1035 cm^{-1}	(-C-O-C- stretching (sym.) in alkanyl ether)
	1472 cm^{-1}	(-C-H- deformation in methylene)
	790 cm^{-1}	(1,4-Disubstituted benzene)
	887 cm^{-1}	(1,2,4,5-Tetrasubstituted benzene)
	3168 cm^{-1}	(-NH- stretching in pyrimidine)
	2938 cm^{-1}	(-S-CH ₂ - stretching in thioether linkage)
	745 cm^{-1}	(-C-Cl- stretching in aromatic ring)

NMR Spectral Data

(TN-15)

No.	Chemical shift δ ppm	Multiplicity	Number of proton (s)	Assignment
1.	3.78	Singlet	2H	-CH ₂ at <u>a</u>
2.	6.67	Doublet	1H	Ar-H at <u>b</u>
3.	6.82	Doublet	1H	Ar-H at <u>c</u>
4.	8.86	Doublet	1H	Ar-H at <u>d</u>
5.	8.88	Singlet	1H	-NH at <u>e</u>
6.	3.87	Triplet	4H	Ar-H at <u>f</u>
7.	2.99	Triplet	4H	Ar-H at <u>g</u>
7.	6.98 to 7.28	Multiplet	7H	Ar-H at <u>h</u> , <u>i</u> , <u>j</u> & <u>k</u>

Antibacterial Activity

This part deals with the in-vitro screening of newly prepared compounds for antibacterial activity. The species *S.aureus*, *E.coli*, *S.typhi* and *B.subtilis* have been taken for the antibacterial activities. Agar-cup method was carried out for the in-vitro screening for antibacterial activity.

The results of the compounds synthesized given for antibacterial screening are mentioned in following table along with standard drugs.

Table . 2 Antibacterial Activity

S. No.	R	(Zone of inhibition in mm) at 50 µg / ml concentration			
		<i>E.Coli</i>	<i>S.Aureus</i>	<i>S.Typhi</i>	<i>B.Subtilis</i>
TN-1	4-CH ₃ ·C ₆ H ₄	---	---	09	10
TN-2	4-N(CH ₃) ₂ ·C ₆ H ₄	12	11	10	08
TN-3	2-OH·C ₆ H ₄	12	09	11	---
TN-4	4-OH·C ₆ H ₄	10	09	---	09
TN-5	4-Cl·C ₆ H ₄	10	13	09	10
TN-6	2,4-(Cl) ₂ ·C ₆ H ₃	12	13	12	09
TN-7	4-F·C ₆ H ₄	11	11	---	---
TN-8	2-OCH ₃ ·C ₆ H ₄	10	07	09	08
TN-9	4-OCH ₃ ·C ₆ H ₄	13	12	11	10
TN-10	3,4,5-(OCH ₃) ₃ ·C ₆ H ₂	14	09	---	---
Standard	Tetracycline	15	19	24	21
Drug	Chloramphenicol	18	25	24	20

Conclusions

The antimicrobial screening results reveals following points. In the synthesised compounds, some compounds showed moderate to good activity against the entire microorganisms whereas some compounds were found inactive. In comparison with standard drugs compounds TN-1 & TN-10 showed maximum zone of inhibition against *E.coli*, *S.aureus*, *S.typhi* and *B.subtilis*. In detail the compound TN-2 have good activity against *E. coli*. Compound TN-6 & TN-10 have good activity against *S.Aureus* while compound TN-5 & TN-7 against *S.Typhi* and TN-7 against *B.Subtilis* have found modest activity compared to the standard drugs. The above activities are quite interesting and further study in the molecule is essential.

Thus from above discussion it may be concluded that it is worthwhile to pursue further investigation by manipulating the above novel mercapto oxadiazole derivatives.

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