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SYNTHESIS AND ANTIMICROBIAL STUDY OF SOME NOVEL QUNO AND PYRANO FUSED THIOPYRIMIDONES SUBSTITUTED WITH ACRIDINE

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ABSTRACT

Acridines have been reported to possess fungicidal, bactericidal, antimicrobial activities. Various substituted acridines are known to exhibit significant biological activities, viz., bactericidal and fungicidal *etc*.

1-[Acrinine-9-yl]-4-arylthiosemicarbazides (A) were obtained in basic medium (in presence of pyridine) by reaction of 9-chloroacridine and arylthiosemicarbazide. 1-[Acridine -9-yl]amino -3-aryl-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-diones (B) were obtained in acidic medium. 1-[Acridine-9-yl-1,2,3-trihydro-5-oxo-2-thioxo-4aH,5H-quino[2,3-d] pyrimidin-4-one (C) were obtained in presence of anthranilic acid and fused sodium acetate. 1-[Acridine-9-yl]amino-3-aryl-5-methyl-1,2,3-trihydro-7-oxo-2-thioxo-7H-pyrano[2,3-d] pyrimidin -4-one were obtained in acidic medium .

All the compounds (A,B,C,D) were characterised by ir, nmr and mass spectroscopic methods and screening was done for their antimicrobial activities. The screening revealed good to moderate level of activity.

Keywords: Acridine, Antimicrobial, Arylthiosemicarbazides, 9-Chloroacridine, Pyrano, Quino.

INTRODUCTION

Billions of rupees worth of growing crops are lost to weeds, insects, diseases and rodents annually. In the previous years, the incidence of microbial infection has increased on alarming levels over the world as result of antimicrobial resistance. The health problem demands to search and synthesise a new class of antimicrobial compounds effective against pathogenic microorganism that have developed resistance to the antimicrobial compounds used in current regimen.

The therapeutic importance of acridines is well documented. Among these are simple molecules including 9-substituted oxyacridines and 1,2,3,4-tetrahydroacridine derivatives. For

instance, some biheterocyclic compounds consisting of 9-thioacridines and 9-thio-1,2,3,4-teterahydroacridanones has been synthesised which are potent antimicrobials.

CHEMISTRY

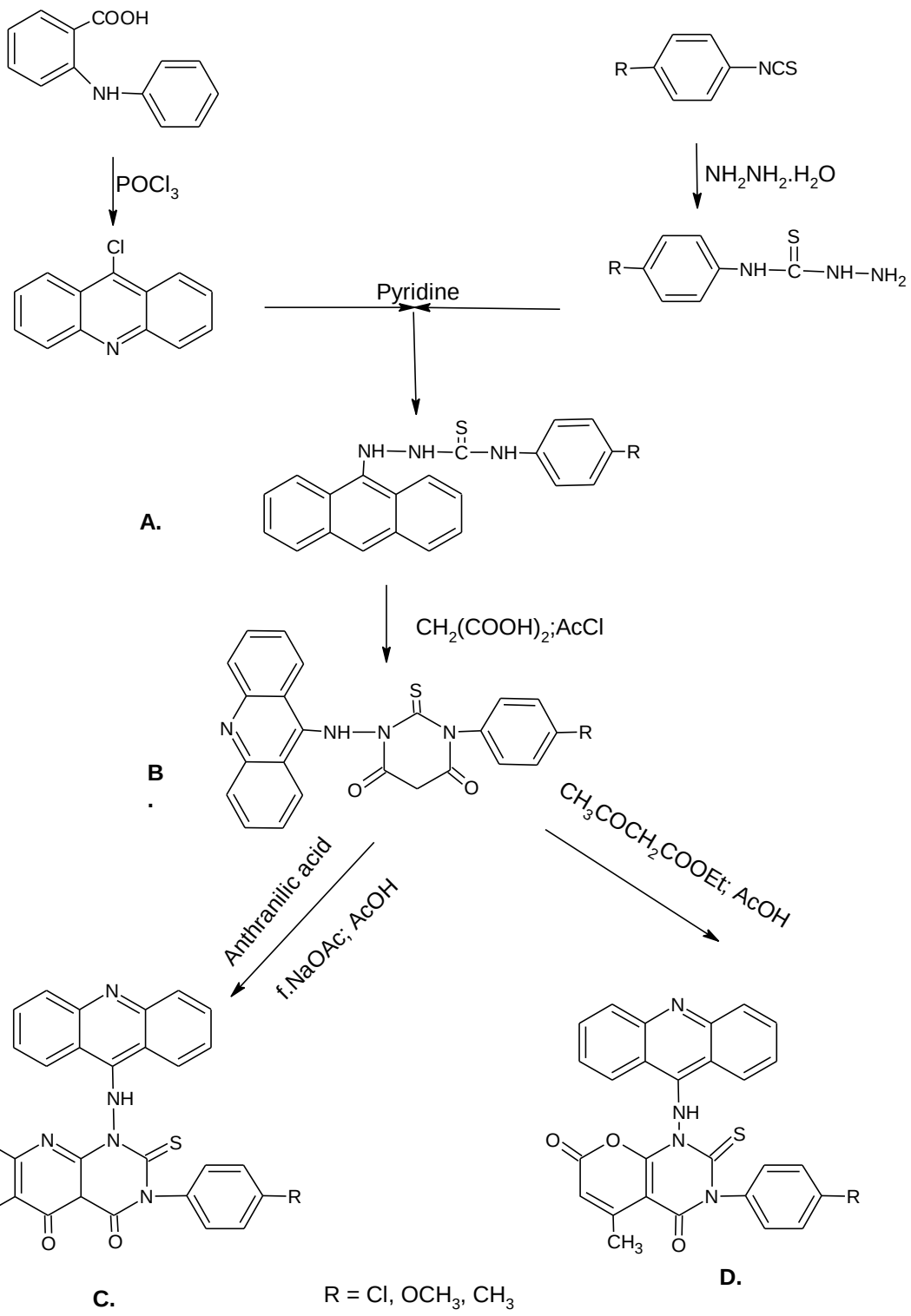
In the present study four groups of compounds have been synthesised, characterised and screened against a fungus (*A.niger*) and a bacteria (*E.Coli*) [i]. All the compounds were purified by recrystalisation. At all levels the compounds were analysed with element detection and spectroscopy. All reactions comprise of simple condensation reactions at reactive methylene (enol) sites. These procedures provide novel methods of preparing fuesd rings- pyrano(bicyclic) and quino(tricyclic). These fused thiopyrimidones when substituted with acridine moiety were expected to enhance antimicrobial activities to a greater extent. At the end of experiment these presumptions were found true[ii].

Antimicrobial screening doesnot show much promising results. However,a chloro group on the ortho position of phenoxy moiety substantially increases the activity [iii]. A combination of methoxy group on the phenyl ring increases activity to further extent. If not better, these compounds are quite comparable with Blitox 50 WP, Gentamycine and Ciproflaxacin[iv].

RESULT AND DISCUSSION:

The elemental analysis is carried out for each compound in the series. The percentage of CHNS show close coherence with the expected molecular formula of the compounds predicted to be formed from the known procedures. Formation of (A) group of compounds is clearily indicated by IR and MASS spectra IR spectra exibit the characteristic peaks δ_{max} cm^{-}of groups N-H (3400), C-N (1080,1010) C-Cl (770), mass spectra show the base peak (100%)at m/z=195 which corresponds to the peak obtained by the fragment formation of this peak is much in accordance with the fragmentation [v]. Formation of compound (B) group of compounds were again analysed by IR spectra. Which gave prominent peak at δ_{max}cm^{-1} for β-diketone along with other usual peaks N-H (3060), C-N (1580), C-S, (1200), C-Cl(770)[vi]. As we proceed to the formation of compounds of (C) and (D) groups the peak of β-diketone (1680cm^{-1}) disappears indicated > that the condensation reactions had taken place at this site. One carbonyl group CO group remains isolated giving peak at 1600cm^{-1} along with other usual peak C-N (1260), C=S (1160) =C-CH_3 (1020)[vii]. The NMR peaks very well fit in the proposed structure of these compounds proving that the compounds have been actually formed.

SCHEME


COOH
NH
POCl3
Cl
N
R
NCS
NH2NH2.H2O
S
NH—C—NH—NH2
Pyridine
NH—NH—C—NH
S
R
A.
CH2(COOH)2;AcCl
B.
Anthranilic acid
f.NaOAc; AcOH
CH3COCH2COOEt; AcOH
O
CH3
C.
D.
R = Cl, OCH3, CH3

Antimicrobial activity:

All the compounds of the series have screened against *A. flavous* and *E. coli.*

Antimicrobial screening:

The compound show moderate level of antifungal activity a substituent of aryl moiety affect the activity in the following order. -OCH_3, -Cl, -CH_3. Fusion quinine nucleus on thiopyrimidine ring enhance the activity while fusion of pyran failes[viii] to do so. A substituent of aryl moiety affects the activity in the following order.

$OCH_3 > Cl > CH_3$.

Antibacterial screening: compounds almost show 1-6 almost inactive and 7-12 show moderate level of activity (Table 1).

Table 1. Antibacterial screening

S.No.	Series	Compound No.	R	Average % inhibition after 168 hour. Organism: *A.flavus* concentrations (ppm)			Average % inhibition after 36 hours. Organism: *E.coli* concentrations (ppm)		
				1000	**100**	**10**	**1000**	**100**	**10**
1.	**A**	1	-Cl	78	**52**	41	40	30	21
		2	-OCH_3	80	**55**	40	45	33	19
		3	-CH_3	68	48	38	38	25	16
2.	**B**	4	-Cl	77	60	39	41	31	12
		5	-OCH_3	81	54	40	44	33	15
		6	-CH_3	70	45	37	39	24	12
3.	**C**	7	-Cl	72	69	55	50	45	37
		8	-OCH_3	74	78	61	56	50	39
		9	-CH_3	70	65	44	49	41	28
4.	**D**	10	-Cl	78	53	33	50	39	25
		11	-OCH_3	81	50	30	57	43	38
		12	-Cl	70	52	34	49	29	21

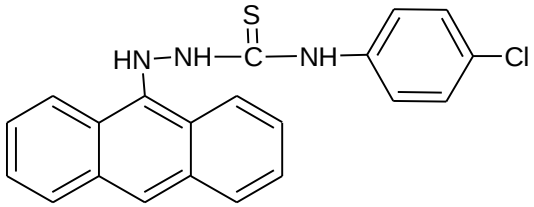
Experimental:

1. **Instrumentation and methodology**

   Charactrised by elemental analysis (Carlo Erba 1108 Heraeus), Infrared (KBr, Nujol, perkin Elmer-R-32-spectrometer, 90MHZ, TMS) and mass (jeol D-300) spectra, melting point were taken in open capillaries. Due to limited facilities available compounds were screened for their antifungal against ***A.fiavus*** and antibacterial against ***E.coli*** activities[ix]. Their antifungal activities against A.flavous[x] involving mixing of toxicants with agar medium and then inoculating a fungus colony on such poisoned food to grow. The antifungal activity of each compound was screened at three different concentrations viz., 1000, 100, and 10ppm. The compounds were tested in acetone solution. One standered solution (1% w/v) of each compound was prepared and 1.0

solution of this solution was diluted by 9.0ml and 99.0ml of the solvent. In this way three solutions of concentrations 1000,100,10 were obtained[xi].

2. General method for the synthesis of compound (A):

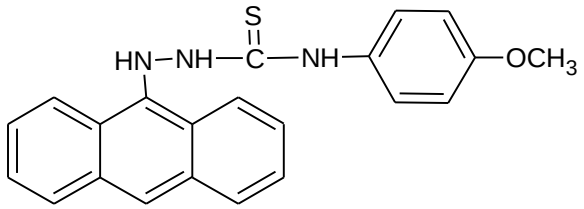


(1) A mixture of 9-chloroacridine (2.14 g; 0.01M) p-chlorophenyl thiosemicarbazide (2.02g; 0.01M) and pyridine (5.00ml) was refluxed for four hour and cooled. The resulting mass was poured into water, acidified with dilute hydrochloric acid, kept overnight and filtered. Solid thus obtained was washed and recrystallised from hot aqueous ethanol[xii].

M.p. 145^0 , yield 2.97 g (78%)
Analysis: C 63.13, H 3.80, N 14.16, S 8.30, $C_{20}H_{15}ClN_4S$ Found

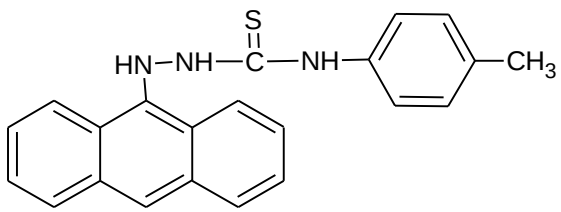
(2) 9-chloroacridine 2.14 g, p-Methoxypheny thiosemicarbazide 1.97 g, pyridine 5.00 ml , time of reflux 4:00 hour.

M.p 130^0 , yield 3.70 g (99%)
Analysis: C 67.11, H 4.62, N 14.74, S 8.15, $C_{21}H_{18}N_4OS$ Found



(3) 9-Chloroacridine 2.14 g, p- Methyl phenyl thiosemcarbazide 1.81 g, pyridine 5.00 ml time of refluxed 4.00 hours.

M.p 160^0 , Yield 3.22 g(90%)
Analysis: C 70.39, H 4.89, N 15.13, S 8.86 %; $C_{21}H_{18}N_4S$ Found

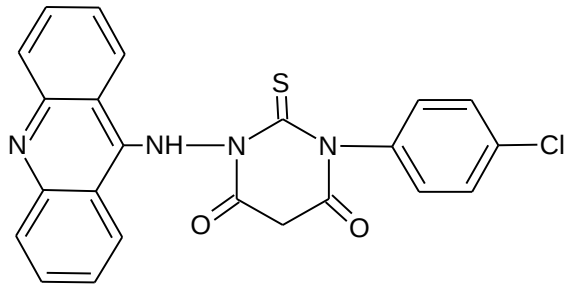


3. Genral method for synthesis of Synthesis of compound (B):

(4) 1-(Acridine-9'-yl)-4-P-chlorophenyl thiosemicarbazide (3.58 g, 0.01M), malonic acid 1.35 g and 5:00ml of acetyl chloride were gently heated for four hour on a waterbath and cooled. The resulting mass was poured into cold water, stirred well, kept overnight and filtered. The residue was washed with water, dried and recrystallised from aqueous ethanol[xiii].

M.p. 210^0, yield 2.04 g 90%

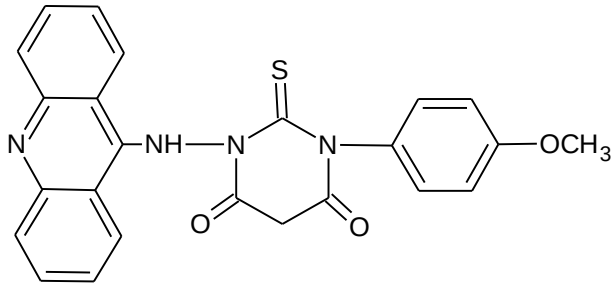
Analysis: C 61.79, H 3.29, N 12.46, S 7.00; $C_{19}H_{16}ClN_3O_4S$ Found



(5) 1-(Acridine-9'-yl)-4-Pmethoxyphenyl thiosemicarbazide (3.74 g), malonic acid (1.35),Acetyl chloride 5.00 ml time of reflux 4:00 hours

M.p. 173^0 Yield 1.42 g 32%

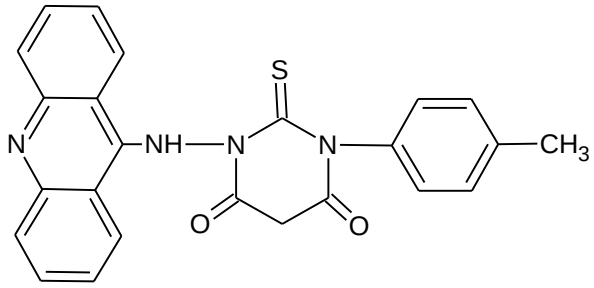
Analysis: N 12.54, S 7.10; $C_{24}H_{18}N_4O_3S$ Found



(6) 1-(Acridine-9'-yl)-4-P-methyl phenyl thiosemicarbazide (3.74 g), malonic acid (1.35), Acetyl chloride 5.00 ml time of reflux 4:00 hours

M.p. 180^0 Yield o.78 g 18%

Analysis: N 12.99, S 7.48; $C_{24}H_{18}N_4O_2S$

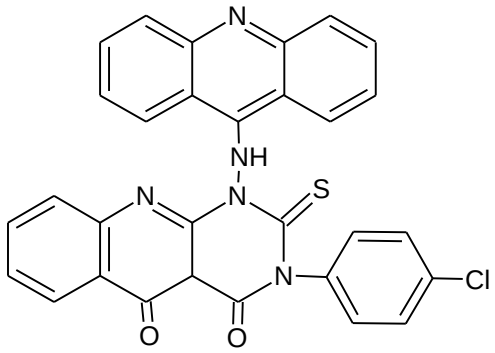


4. General method for synthesis of Synthesis of compound(C) :

(7) A mixture of 1-[Acridine-9'-yl] amino -3- (4'-methyl phenyl) 1,3-dihydro -2-thioxo-2H,5H-pyrimidine-4,6-dione (2.13g 0.005M) ,Anthranilic acid (1.47 g)Glacial acetic acid (5:00 ml) and fused sodium acetate (2:00 g)was refluxed for four hour. After cooling the contents were poured into cold ammonia and stirred, filtered, washed and recrystallized from aqueous ethanol[xiv].

M.p 210^0 yield 2.25 g (86%)

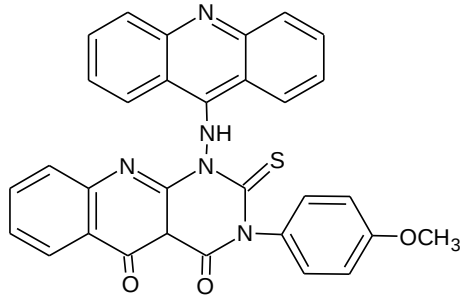
Analysis: C 70.55, H 3.97, N 13.24, S 6.04 $C_{31}H_{21}N_5O_2S$ Found



(8). A mixture of 1-[Acridine-9'-yl] Amino -3- (4'-methoxyphenyl) 1,3-dihydro -2-thioxo-2H,5H-pyrimidine-4,6-dione (2.13g 0.005M), Anthranilic acid (1.47 g)Glacial acetic acid (5:00 ml) and fused sodium acetate (2:00 g)was refluxed for four hour. After cooling the contents were poured into cold ammonia and stirred, filtered, washed and recrystallized from aqueous ethanol.

M.p 190^0 yield 2.84 g (86%)

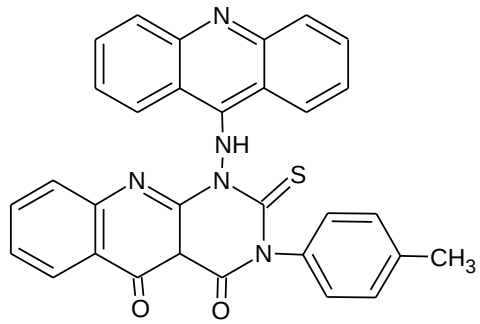
Analysis: N 12.81, S 5.82, $C_{31}H_{21}N_5O_3S$ Found



(9). 1-[Acridine-9'-yl] Amino -3- (4'-chloroyphenyl) 1,3-dihydro -2-thioxo-2H,5H-pyrimidine-4,6-dione (2.13g 0.005M), Anthranilic acid (1.47 g)Glacial acetic acid (5:00 ml) and fused sodium acetate (2:00 g) Time of refluxed 6 hour

M.p 210^0 Yield 2.84 g (86%)

Analysis: N 12.70, S 5.84, $C_{30}H_{18}ClN_5O_2S$ Found

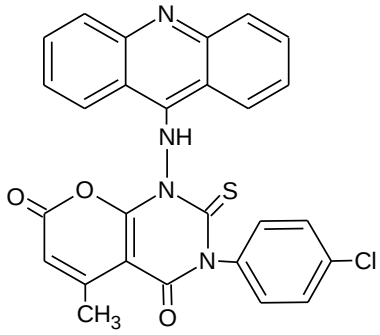


5. General method for synthesis of Synthesis of compound(D):

(10). A mixture of 1-(acridine-9'-yl)amino-3-(4'- chlorophenyl)-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-dione (0.005M), glacial acetic acid(0.005ml), ethylacetoacetate (0.005M),time of reflux 6 hours.

Yield 1.78g(60%), M.P. 204^0

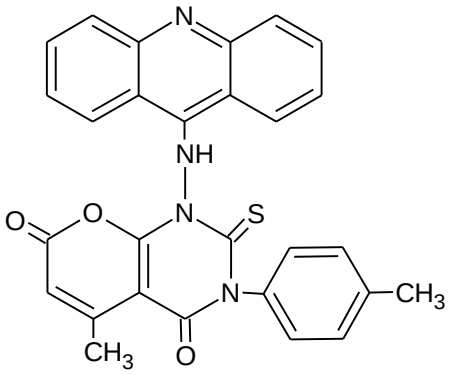
Analysis: C 63.02 , H 3.24, N 10.87, S 6.20, $C_{27}H_{17}ClN_4O_3S$ found



(11). A mixture of 1-(acridine-9'-yl)amino-3-(4'- chlorophenyl)-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-dione (0.005M), glacial acetic acid(0.005ml), ethylacetoacetate (0.005M),time of reflux 6 hours.

Yield 1.86g(73%), M.P. 180^0

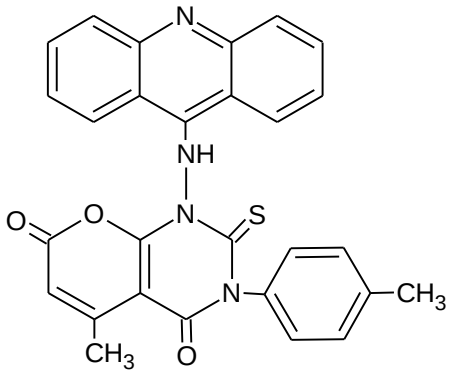
Analysis: N 10.97, S 6.29, $C_{28}H_{20}N_4O_4S$ Found



(12). A mixture of 1-(acridine-9'-yl)amino-3-(4'- chlorophenyl)-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-dione (0.005M), glacial acetic acid(0.005ml), ethylacetoacetate (0.005M),time of reflux 6 hours.

Yield: 1.76g(71%, m.p. 215^0

Analysis: N 11.24 S 6.46 $C_{28}H_{20}N_4O_3S$ Found



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