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Study of biological activity of some new 1, 2, 4-triazine derivatives & 1, 2, 4- trazole derivatives

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Abstract
In this paper, we have describe the synthesis and antibacterial activities of a new heterocyclic compounds 2–6. Thesis compounds showed in vitro growth inhibitory activity against the tested organisms comparable or higher than streptomycin. The biological data revealed that with slight modifications in the structure on can plan for the drug design.

Keywords: biological and 1, 2, 4- trazole derivatives

Introduction
A large number of aliphatic, alicyclic, aromatic and heterocyclic carbohydrazides, their derivatives and related compounds are reported to present a plethora of biological activities [1]. Thus, different carbohydrazides were found to be useful as medicaments especially in the treatment of inflammatory and autoimnuine diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis. Carbohydrazides and related compounds exhibited antifungal [2], antiviral [3], bacteriostatic [4, 5], antiparasite [6], antituberculous [7], psychotropic, and insecticidal [8] activities. Some heterocyclic carbohydrazides are useful as antifertility agents in rats and pigeons [9]. Other carbohydrazides were reported to be components of deodorant compositions that can be used for removal of offensive odor components [10]. In the last decade numerous 1, 2, 4-triazine derivatives have been synthesized and screened in vitrolvivo, thus revealing their varied biochemical, biological, pharmacological or cellular activities [11]. These facts encouraged us to synthesize some new 1, 2, 4-triazine derivative, their derivatives in anticipation of expected interesting biological activities.

Materials and Methods
Synthesis of N- anthracen-9(10H)-vlidene-4-niethvlpyridine-2-ainine 2
A mixture of anthrone (0.012 mol), 15 ml glacial acetic acid and 2-amino-4-methylpyridine (0.012 mol) was heated under reflux for 10 hrs. The reaction mixture was filtered off and recrystalized from ethanol.

Synthesis of 2-anthraces-9(10H)-ylideneamino)-4- carboxylic acidpyridine 3
Compound 2 (0.05 mol) is added to a solution of (0.05 mol) of potassium permanganate and (0.05 mol) of sodium carbonate in (25 ml) water and the mixture is heated under reflux until the color of the permanganate has disappeared (15 hrs). The reaction mixture was filtered while still hot to get rid of the Mn02 precipitate. The cooled filtrate is acidified with sulphuric acid (20%), the carboxylic acid precipitate is filtered off, washed with a little cold water and used without further purification.

Synthesis of ethyl 2-(anthraces-9 (10H)-ylideneamino)pyridine -4-carhoxylate 4
A mixture of the acid 3 (0.01 mol), abs. ethanol (10 ml), and few drops of conc. sulfuric acid was refluxed for 10h, the reaction mixture was cooled to room temperature and then in the refrigerator for 5 hrs. The solid product was filtered off washed and recrystalized from ethanol.

Synthesis of 2-(anthraces-9(10H)-ylldeneamino)pyridine-4-carbohydrazide 5
A mixture of ester 4 (0.012 mol) and hydrazine hydrate (0.02 mol) was refluxed for 5 hrs, Then abs. ethanol (15 ml) was added and refluxed for further 8 hrs.

The separated precipitate was filtered and washed with cold water.

Synthesis of 2-4-(anthracen-9(10H)-ylideneamino)-4-0, 6-dihydro-L2, 4-rriazin-5(2H)-one)pyridine 6

Compound 5 (0.01 mol) and chloroacetamide (0.01 mol) were mixed together in (20 ml) abs. ethanol. The reaction mixture was refluxed for 24 hrs, the solvent was reduced to one third its volume under reduced pressure. The crude product was obtained by filtration, washed with water and recrystalized from chloroform.

Results and Discussion

Synthesis and physical properties

The 2-(4-(anthracen-9 (10H)-ylideneamino)-4- (1, 6-dihydro-1, 2, 4-triazin-5(2H)-one)- pyridine 6 was prepared by the reaction of anthron 1 with 2- arnino-4-methylpyridine in glacial acetic acid to give N-anthracen-9 (10H)-ylidene-4-methylpyridine-2- amine 2. Oxidation of compound 2 using $KMnO_4$ gave 2-(anthracen-9(10H)-ylideneamino)-4-carboxylic acidpyridine 3 which converted to the target product through its reaction with EtOH and hydrazine hydrate, respectively, Scheme 1:

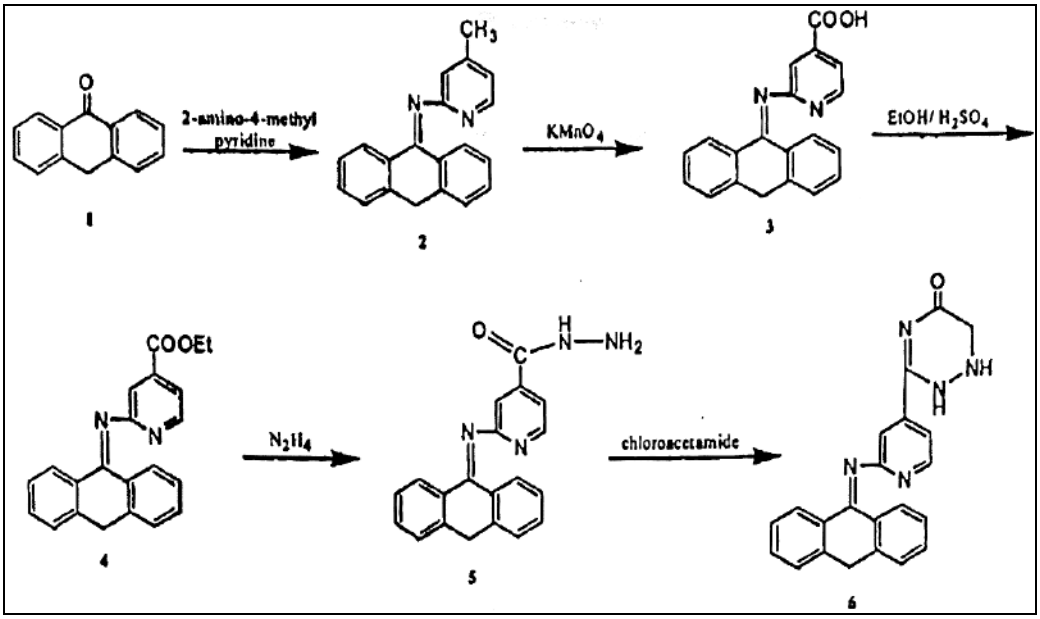


Fig 1: Scheme 1

The purity of the synthesized compounds was checked by TLC using silica gel-G as adsorbent further evidence for the characterization of the synthesized compounds was obtained from C, H and N analysis, which are in argent with the calculated values, Table 1.

Infra-Red spectroscopy

The FTIR spectrum of N-anthracen-9(10H)-ylidenehistidine 2 showed disappearance of ketone C=0 bands at 1715 cm^{-1} which confirm the conversion of compound 2 to 2-(anthracen-9(10H)-ylideneamino)- 4-carboxylic acidpyridine 3. On the other hand, the FTIR spectrum of compound 3 has carboxylic acid C=0 stretching vibration at 1735 cm^{-1} [12]. In the spectra of ethyl 2-(anthracen-9 (10H) ylideneamino) pyridine -4-carboxylate 4, 2- (anthracen-9 (10H)-ylideneamino)pyridine-4-earbohydrazide 5 and 2-(4-(anthracen-9 (10H) ylideneamino)-4- (1, 6-dihydro-1, 2, 4-triazin-5 (2 H) one) pyridine 6, the bands at 1723, 3324-3256 and 1685 cm-1 were assigned to the stretching of ester C=0, -$NHNH_2$ and amide C=0 groups, respectively. Table 2 lists the stretching frequency (u) for some of the characteristics groups exhibited by the synthesized compounds.

Nuclear magnetic resonance

The ^{1H}NMR spectra for all compounds were recorded in [$^{2}F^{16}$] OMSO using tetramethysilane as the internal standard. The data are compiled in Table 3. The conclusion drawn from ^{1H}NMR studies of the synthesized compounds lend further support to suggested formation of 2-(4-(anthracen-9 (10 H) ylideneamino)-4-(1, 6-dihydro-1, 2, 4-triazin-5(2 H) one) pyridine 6. The most characteristic evidence support the formation of compound 6 was the two singlet peaks at 5 8.40 and 8.53 ppm due to the N-H protons, which further characterized by D_2O exchange. Furthermore, there are a multiple signals of the aromatic protons resonances at 6.42-7.89 ppm [13].

Table 1: Physical data for the synthesized compounds

Comp	Color	% Yield	M.P.C.	Molecular Formula	Found (Calcd. %)		
					C	H	N
1.	Brown	–	152–154	$C_{18}H_{24}O$	84.99 (84.32)	8.72 (9.444)	–
2.	Yellow	77	92–94	$C_{25}H_{34}N_2$	8.343 (82.82)	10.01 (9.45)	8.56 (7.73)
3.	White	83	126–128	$C_{24}H_{32}N_2O_2$	77.56 (76.49)	9.13 (8.22)	6.32 (7.14)
4.	Light pink	72	102-104	$C_{27}H_{36}N_2O_2$	76.38 (77.10)	9.24 (8.60)	7.14 (6.66)
5.	Brown	90	188-190	$C_{25}H_{34}N_4O$	72.29 (73.85)	7.39 (8.41)	12.92 (13.78)
6.	White	87	89-91	$C_{29}H_{43}N_5O$	73.41 (72.92)	10.31 (9.07)	13.92 (14.66)

Table 2: Physical data for the synthesized compounds

Comp.	O–H	–NHNH$_2$	N–H	Aromatic Protons	Aliphatic Protons	C=O	C=N
1	–	–	–	3056	–	1715	–
2	–	–	–	3069	2943, 2857	–	1610
3	3421	–	–	3054	–	1735	1611
4	–	–	–	3067	2952, 2864	1723	1612
5	–	3324–3256	3172	3063	–	1680	1610
6	–	–	3176	3060	–	1685	1613

Table 3: ^{1}HNR data (δ, ppm) of all compounds prepared

Comp.	–CH$_3$	–CH$_2$–	Aromatic Protons	N–H	–NH$_2$	O–H
1	–	–	6.77–7.98	–	–	–
2	1.34	–	6.56–7.78	–	–	–
3	–	–	6.58–7.83	–	–	9.54
4	1.52	2.03	6.57–7.75	–	–	–
5	–	–	6.54–7.62	8.42	8.89	–
6	–	–	6.56–7.70	8.40, 8.53	–	–

Table 4 shows the most relevant ^{13}NMR data. Due to scan solubility of the synthesized compounds, their spectra were recorded in [$_2$H^6] DMSO. The –CH$_3$ peak of N-anthracen-9(10H)-ylidene-4-methylpyridine-2-amine 2 appeared at 12.63 ppm. Furthermore, the C=O resonances group of 2-(anthracen-9 (10H)-ylideneamino)-4-carboxylic acidpyridine 3, ethyl 2-(anthracen-9 (10H)-ylideneamino)pyridine -4-carboxylate 4, 2-(anthraces- 9 (10H)-ylideneamino) pyridine-4-carbohydrazide 5 and 2-(4-(anthracen-9(10H)-ylideneamino)-4-(1,6- dihydro-1,2,4-triazin-5 (2 H)-one)pyridine 6 appeared at 173.46, 171.25, 170.26 and 169.83 ppm, respectively [14].

Antimicrobial activity

All the compounds 1-6 were in vitro screened for their antibacterial activity against Gram-positive (Staphylococcus aureus ATCC 6538p Staphylococcus epidermidis ATCC 12228 and Bacillus subtilis PTCC 1023) and Gram-negative (Escherichia coil ATCC 8739, Klebsiella pneumoniae ATCC 10031, and Pseudomonas aeruginosa ATCC 9027) bacteria by the drug diffusion method [15]. The zone of inhibition was measured in mm and was compared with standard drug. DMSO was used as a blank and Streptomycin was used as antibacterial standard. All the compounds were tested at 100 µg/ml and 250 µ/m1 concentration. The data are summarized in Table 5, and show that all compounds display certain antibacterial activity.

Table 4: ^{13c}NMR data (8, ppm) of all compounds prepared

Comp.	–CH$_3$	–CH$_2$–	–C=N–	Aromatic Protons	C=O
1	–	13.47	–	134.16–142.85	170.12
2	12.63	13.31	40.15	133.67–143.29	–
3	–	13.42	41.13	132.68–142.20	173.46
4	12.54	13.38, 13.89	40.89	133.35–144.21	171.25
5	–	13.43	40.76	134.39–143.22	170.26
6	–	13.46	40.78	132.65–142.89	169.83

Table 5: Antibacterial activity of all compounds prepared

Comp.	Zone of inhibition in mm											
	S. Aureus		S. Epidermids		B. Subtilis		K. Pneumonie		E. Coli		P. Aeruginosa	
	100µg	200µg	100µg	200µg	100µg	200µg	100µg	200µg	100µg	200µg	100µg	200µg
1	–	–	–	–	–	–	–	–	–	–	–	–
2	+	+	+	+++	++	++	++	++	+++	++	++	++
3	++	+++	+	+	+	+++	++	++	+	+	++	++
4	+	+	++	+	++	+	+	+	++	+++	+++	+
5	++	+	+	+++	+++	++	+	+		+	+	+
6	+++	+++	++	++	++	+++	+++	++	+	+	+	+++
Streptomycin	+	+	++	+	+	+	+	++	+	+	+	+

+++ = high activity, ++ = moderate activity, + = low activity, – = no activity

Synthesis of 124-triazolederivatives

The azole moiety is an important and frequent insecticidal, agrochemical structural feature of many biologically active compounds such as cytochrome P450 enzyme inhibitors and peptide analog inhibitors. Recently, much attention has been focused on 1 H-1, 2, 4-triazole derivatives for their broad-spectrum activities, such as fungicidal, herbicidal, anticonvulsant and plant growth regulatory activities. Further, the substituted 1, 2, 4-triazole derivatives were also reported to show antifungal, insecticidal, herbicidal and anti-inflammatory properties which were similar to 1H-1, 2, 4-triazole derivatives. Promoted by the above observations that the combination of two or more heterocyclic and non-heterocyclic systems enhances the biological profile many-fold than its parent nuclei, we considered to synthesize some compounds bearing 1H-1, 2, 4-triazole in a molecular framework. 3(2H)-Pyridazinones and their derivatives have been reported having fungicidal, insecticidal and pharmacological activities. Some of them showed similar activity as JH, such as NC-170 and NC-184. (Scheme 1)

Taking these structural features into consideration, it was thought worthwhile to synthesize the novel compounds that combining the 1, 2, 4-triazole with 2-t-butyl-4, 5-5 ichloro-pyridazinone by sulfur heteroatom.

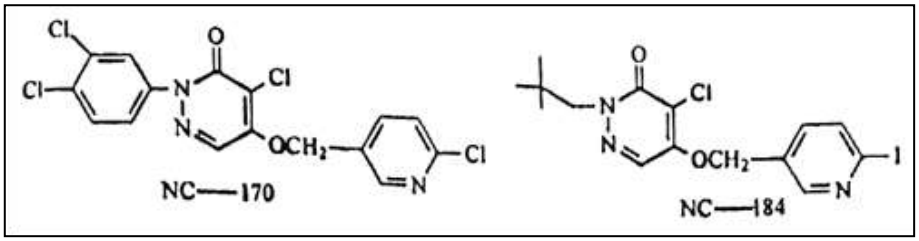
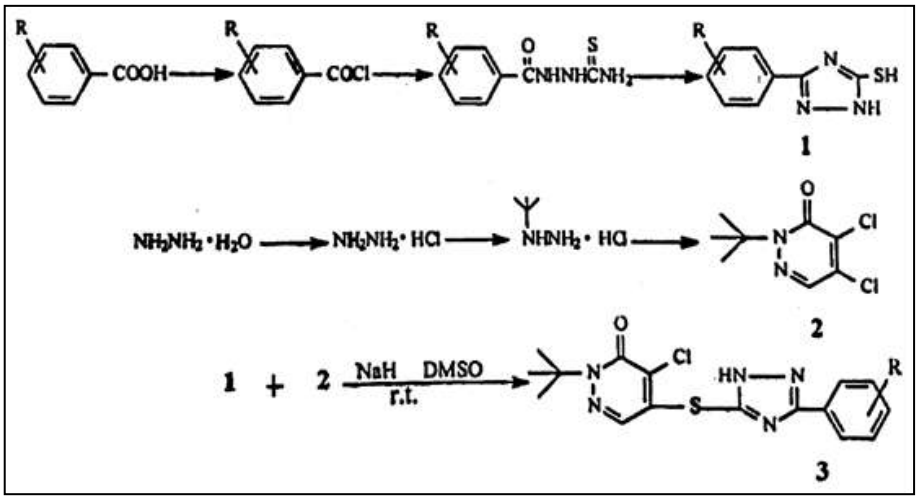


Fig 2: Scheme 1: Some of them showed similar activity as JH, such as NC-170 and NC-184



3a R = H; 3b R = 2-OCH_3 3c R = 4-NO_2 3d R = 3-NO_2 3e R = 4-OCH_3 3fR = 3, 5-2 CH_3 3g R = 4-F; 3h R 3-F

Fig 3: Scheme 2: The synthetic route of the title compounds was seen in Scheme 2.

The intermediates, 1 and 2, were synthesized according to the literature and got the accept yield. The synthetic conditions of the title compounds were investigated, such as temperature, time and base. The temperature had great effect on the yield of the title compounds. The low temperature will prolong the reactive time, otherwise, the by-product will become more when the temperature is beyond 40 °C. We hold the room temperature about 30 °C and got the satisfied yield. The effect of strong base was better than that of weak base clearly.

Conclusion

All the title compounds' bioactivity was screened by the method of leaf-dip. A stock solution of title compounds (1000 ppm) in DMSO was used for preparing various concentrations for bioactivity screening. The compounds of 3d, 3e and 3g showed insecticidal activity against Aphis rumicis Linnaeus. They have the insecticidal rate 45%, 38% and 30% at the concentration of 500 ppm. The insecticidal activity decreased clearly when the concentration was decreased.

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