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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW4-(SUBSTITUTED\ARYL)-((1, 3–DIPHENYL-1H-PYRAZOLE-4-YL) METHYLENEAMINO)-1, 5-DIMETHYL-2-PHENYLPYRAZOLILDIN-3-ONE DERIVATIVES

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ABSTRACT

Schiff Base derivatives are important class of compounds. They possess different types of Biological activities like antibacterial, antiviral, anti HIV, antifungal etc. Schiff base derivatives are prepared by the condensation of aldehyde and amine and these compounds are characterized by chemical and instrumental methods. Their important biological properties have been investigated.

INTRODUCTION: Hydrazones, possessing an azomethine –NHN=CH- proton, constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Hydrazones are synthesized by heating the appropriate substituted hydrazine /hydrazides with aldehydes and ketones in solvents like ethanol, methanol, butanol, glacial acetic acid, ethanol-glacial acetic acid. These are well known intermediates for the preparation of oxadiazolines, azetidinones, thiazolidinones and many other derivatives.

Hydrazones exhibit a wide range of pharmacological activities like Anti-cancer [1], Anti-malarial [2], and Anti-tubercular [3] etc.

A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like Anti HIV [4], Antiviral [5], Ant parasitic [6] etc. Schiff base of 4-amonoantipyrine have a variety of applications in biological, clinical, analytical and pharmacological areas. Studies of a new kind of chemotherapeutic Schiff bases are now attracting the attention of biochemists. Earlier work reported that some drugs showed increased activity.

Deoxyriboncleic acid (DNA) is the primary target molecule for most anticancer and antiviral therapies according to cell biologists.

MATERIALS AND METHODS: The compounds N-[(1, 3 –diphenyl-1H-pyrazol-4-yl)methylene- 4H-(1, 2, 4 triazol-3-amine (I_{a-m}) were obtained by following preparation method(I-a) (**figure 1**).

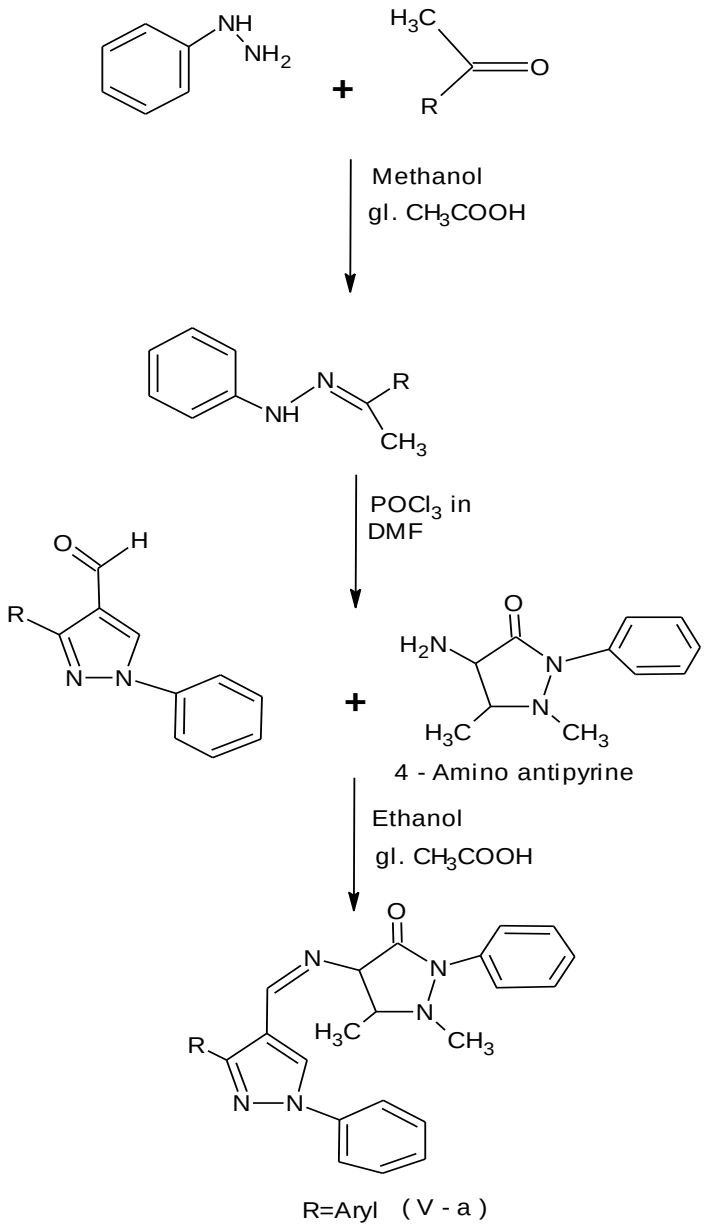

FIG. 1: SCHEME FOR SYNTHESIS OF PREDICTED COMPOUNDS

Synthesis of n- phenylamino- α- methyl- phenyl azomethine: A mixture of phenyl hydrazine (1.08gm, 0.01M) and aceptophenone (1.20gm, 0.01M) in absolute ethanol was refluxed in water bath for 4 hrs in presence of 1ml glacial acetic acid. Product obtained after cooling was crystallized from absolute ethanol [7].

Yield, 1.8gm (90%), M.P.: 64°C. ($C_{14}H_{14}N_2$; Calculated: C, 80.00; H, 6.66; N, 13.37%; Found: C, 79.92; H, 6.64; N, 13.34%).

This typical experimental procedure was followed to prepare other analogs of this series.

Synthesis of 1, 3- diphenyl- 1h- pyrazole- 4- carbaldehyde: N-Phenylamino-α-methyl-phenyl azomethine (0.84gm, 0.004M) was added in a mixture of Vilsmeier – Haack reagent (prepared by drop wise addition of 1.2ml $POCl_3$ I ice cooled 10ml DMF) and refluxed for 6hrs. The reaction mixture was poured into crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from methanol [7].

Yield, 2.16gm (87%), M.P.: 120°C. ($C_{16}H_{12}N_2O$; Calculated: C, 77.42; H, 4.48; N, 11.29%; Found: C, 77.39; H, 4.80; N, 11.28%). Exactly similar experimental

procedure was followed to prepare other analogs of this series.

4-((1, 3–diphenyl-1h-pyrazol-4-yl) methyleneamino)-1, 5-dimethyl-2-phenylpyrazolildin-3-one: A mixture of 1, 3-diphenyl-1H-pyrazole-4-carbaladehyde (2.48gm, 0.01M) and 4-Amino Antipyrine (2.03gm, 0.01M) was taken in absolute ethanol and few drops of glacial acetic acid was added. Then the mixture was refluxed for 6h on water bath. The separated solid was filtered, washed and recrystallized from ethanol [8].

M.P. 127°C, Yield 89%, and $C_{27}H_{25}N_5O$; Calculated: C, 74.39; H, 5.78 N, 16.08; Found: C, 74.30; 1H, 5.75; N, 16.05%).

The same experimental procedure was utilized to prepare other analogs of this serial (Ia-m). Their physical constant data are given in **Table 1**.

TABLE 1: PHYSICAL AND CHEMICAL CHARACTERISTICS OF 4-((1, 3-DIPHENYL-1H-PYRZOL-4YL) METHYLENEAMONO)-1, 5-DIMETHYL-2-PHENYLPYRAZOLIDIN-3-ONE

Compound No.	R	Molecular Formula	Formula Weight	Solvent for crystallization (Final Step)	% yield Colour	M. P. °C R.F.	% Carbon Found (Calculated)	%Hydrogen Found (Calculated)	% Nitrogen Found (Calculated)
V-a	$-C_6H_5$	$C_{27}H_{25}N_5O$	435.12	Ethanol	89/w	127/0.62	74.30/(74.39)	5.75/(5.78)	16.05/(16.080
V-b	4-Cl-C_6H_4	$C_{27}H_{24}N_5OCl$	471.51	Ethanol	81/w	129/0.56	68.66/(68.71)	5.10/(5.13)	14.75/(14.84)
V-c	2-OH-C_6H_4	$C_{27}H_{25}N_5O_2$	451.20	Ethanol	85/y	175/0.60	71.71/(71.80)	5.53/(5.58)	15.45/(15.51)
V-d	4-OH-C_6H_4	$C_{27}H_{25}N_5O_2$	451.20	Ethanol	82/y	100/0.64	71.75/(71.80)	5.54/(5.58)	15.50/(15.51)
V-e	3-OH-C_6H_4	$C_{27}H_{25}N_5O_2$	451.20	Ethanol	87/y	220/0.67	71.77/(71.80)	5.51/(5.58)	15.47/(15.51)
V-f	4-NO_2-C_6H_4	$C_{27}H_{24}N_6O_3$	480.89	Ethanol	83/y	150/0.70	66.75/(66.81)	4.91/(5.02)	18.67/(18.70)
V-g	3-NO_2-C_6H_4	$C_{27}H_{24}N_6O_3$	480.89	Ethanol	89/y	105/0.65	66.73/(66.81)	4.95/(5.02)	18.68/(18.70)
V-h	4-Br-C_6H_4	$C_{27}H_{24}N_5OBr$	513.19	Ethanol	84/y	202/0.62	63.05/(63.13)	4.70/(4.71)	13.45/(13.48)
V-i	4-CH_3SO_2-C_6H_4	$C_{28}H_{27}N_5O_3S$	513.21	Ethanol	83/w	105/0.64	65.41/(65.47)	5.21/(5.30)	13.41/(13.48)
V-j	2,4diOH-C_6H_3	$C_{27}H_{25}N_5O_3$	467.19	Ethanol	81/y	165/0.62	69.27/(69.35)	5.31/(5.39)	14.91/(14.98)
V-k	2,4-diCl-C_6H_3	$C_{27}H_{23}N_5OCl_2$	507.19	Ethanol	89/w	072/0.60	63.81/(63.88)	4.49/(4.57)	13.71/(13.80)
V-l	4-OCH_3-C_6H_4	$C_{28}H_{27}N_5O_2$	465.21	Ethanol	85/w	170/0.59	72.18/(72.22)	5.81/(5.84)	14.99/(15.05)
V-m	4-$CH_3C_6H_4$	$C_{28}H_{27}N_5O$	449.22	Ethanol	89/w	096/0.60	74.75/(74.79)	5.99/(6.05)	15.04/15.07

y=yellow, w=white

The same experimental procedure was utilized to prepare other analogs of this series (Ia-m). The purity of synthesized compounds was checked by thin layer chromatography (TLC) on silica gel plate using ethyl acetate: cyclohexane (70: 30). Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Perkin-Elmer spectrophotometer RXI using KBr disc. ^{1}H NMR spectra are recorded on in $CDCL_3$ ON a Bruker DRX-400 MHz using TMS as inter standard. The chemical shifts are reported as parts per million (ppm) and ESI MS were determined on Discovery Make Thermo Spectrometer.

The characterization data of compounds (Ia-m) are described in **Table 1.**

RESULTS AND DISCUSSION: The synthesis of 4-((1,3–diphenyl- 1H- pyrazol- 4-yl) methyleneamino)-1, 5-dimethyl-2-henyl pyrazolildin -3-one derivatives (Ia-m) involved the reaction between appropriate 1, 3 – diphenyl- 1H-pyrazole- 4- carbaldehyde (I_{a-m}**)** and 4-Amino Antipyrine as described in the general procedure.

IR spectra showed the C=O stretching vibration peak at 1672.05 cm^{-1} and The Schiff base also confirmed by an intense band of C=N around 1408.49cm^{-1}. The other peaks of IR spectra also prove the structure of hydrazones derivatives. The nuclear magnetic resonance spectra (^{1}H NMR) showed the amine proton (N=C-H) at 9.7896 ppm and (N-CH) at 8.4761 ppm and the mass spectrum of comp. (I-a) shows the $[M]^+$ molecular ion (m/z = 435) a base peak.

Many times, due to collision of secondary ion with sample molecular ion, $[M]^+$ or $[m+1]^+$ is formed and is sometimes prominent base peak, which undergoes less fragmentation. As per the nitrogen rule, it must have even molecular weight, which is 435.12 (isotopic mass). 436 peak is 31 % of 435 $[M]^+$ peak indicating the presence of 28 carbon atoms (confirmed by the rule of thirteen). Fragments showed peaks at m/z 204 [(base peak), 231] and m/z etc.

Antimicrobial Activity (Table 2 & 3): Antimicrobial activity testing was carried out by using Agar cup method. Each purified compound was dissolved in dimethyl sulfoxide (DMSO), sterilized by filtration using sintered glass filter and stored at 4^0C. All the synthesized compounds were screened for their antibacterial and antifungal activities against the *E. coli, P. auregenosa, S. aures, S. pyogenus* and the fungi *C. albicans, A. niger,* and *C. albicans*.

The compounds were tested at 250, 100, 50 and 25 concentration using nutrient agar tubes. The highest dilution showing at least 99 % inhibition is taken as MBC (minimal bactericidal concentration). Control experiments were carried out under similar condition by using gentamycin, ampicillin and chloramphenicol for antibacterial activity and nystatin and greseofulvin for antifungal activity as standard drugs.

- ***E. coli***: In compression the standard drug ampicillin compound v-a, v-h, v-k, v-l, v-m Shows equal or higher antibacterial activity and the compound v-a, v-e, v-k, v-m possess equal antibacterial activity also compared to chloramphenicol.

- ***P. aeruginosa***: Compounds no v-h, v-j and v-m exhibit equal or greater antibiotics activity compare to ampicillin at 250µg/ml concentrations. Compounds v-h and v-m shows equal antibacterial activity against chloramphenicol at 250 µg/ml concentrations.

- ***S. aureus***: The compounds v-a, v-d, v-l shows equal or higher antibacterial activity compared to ampicillin at 250µg/ml concentrations. Compound v-g is equal antibacterial activity against chloramphenicol.

- ***S. Pyrognes***: compounds v-b, v-g, and v-m possess higher or equal antibiotics activity compared to ampicillin at 250µg/ml concentrations. Compounds v-j and v-k exhibit equal antibacterial activity against chloramphenicol.

Antifungal activity (Table 4 & 5): The synthesized heterocyclic compound are do not exhibit antibacterial activity at law concentrations (5µg/ml) when antifungal studies was carried with *A. niger* (Aspergillus), it was observed that no compounds shows equal antifungal activity as the standard drug greseofulvin. Compound v-b shows equal antifungal activity compared to nystatin, when the antifungal study was carried out with *C. albicans*.

The compounds v-f, v-g, v-k and v-I shows equal or higher antifungal activity compared to greseofulvin. In compression the standard nystatin compound v-f and v-g shows equal antifungal activity.

Spectral study of 4-((1, 3–diphenyl-1H-pyrazol-4-yl) methyleneamino)-1, 5- dimethyl- 2- phenylpyrazolildin-3-one (i-a) [isotopic weight = 435.12 g].

IR (KBr) cm^{-1}: 1408.49 (C=N Stretching of Schiff base), 2921.64 (C-H Str. Asym.), 1356.02 (C-H def. sym.), 3124.68 (Ar C-H Stretching), 1591.68 (C=N Str. Of pyrazole ring), 1672.05 (C=O Str antipyrine moiety) and 1299.54 (C-N Str antipyrine moiety).

H NMR ($CDCl_3$) δ (ppm): 9.7896(1 H, –CH=N-), 8.4824 (1H, pyrazol ring), 8.4761 and 7.1851(2H, antipyrine ring) 7.2144-7.7695 (15 H, Ar-H), 2.3693(3H, N-CH3), 1.1318-1.1790(3H, C-CH3).

Mass Spectra (m/z) = 435 $(M)^+$, 436(M+2), 204,231.

TABLE 2: ANTIBACTERIAL ACTIVITY TABLE

Comp. No.	Substituent group R	*E. COLI* MTCC 443					*P. AERUGINOSA* MTCC 424					*S. AUREUS* MTCC 96					*S. PYOGENES* MTCC 442				
		5µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
V-a	$-C_6H_5$	-	15	17	18	22	-	11	14	16	19	-	15	17	20	21	-	13	15	16	20
V-b	$4\text{-Cl-}C_6H_4$	-	11	12	14	15	-	11	12	13	15	-	12	14	15	16	-	14	15	17	21
V-c	$2\text{-OH-}C_6H_4$	-	13	13	18	21	-	10	15	18	21	-	11	14	15	18	-	12	14	18	18
V-d	$4\text{-OH-}C_6H_4$	-	14	14	15	17	-	10	13	15	19	-	14	18	18	20	-	11	15	18	20
V-e	$3\text{-OH-}C_6H_4$	-	12	14	19	22	-	11	14	19	20	-	11	12	15	18	-	11	15	17	21
V-f	$4\text{-NO}_2\text{-}C_6H_4$	-	12	15	15	19	-	12	14	16	21	-	11	14	16	18	-	11	14	17	19
V-g	$3\text{-NO}_2\text{-}C_6H_4$	-	13	15	17	18	-	10	13	14	15	-	16	22	22	24	-	12	14	17	20
V-h	$4\text{-Br-}C_6H_4$	-	14	15	18	19	-	13	17	19	21	-	10	15	16	18	-	11	14	18	21
V-i	$4\text{-CH}_3\text{SO}_2\text{-}C_6H_4$	-	13	13	15	17	-	11	12	15	16	-	11	14	16	17	-	12	13	14	17
V-j	$2,4\text{diOH-}C_6H_3$	-	12	13	15	17	-	13	15	18	19	-	10	13	14	15	-	15	18	19	20
V-k	$2,4\text{-diCl-}C_6H_3$	-	14	17	19	20	-	11	16	19	22	-	10	14	16	18	-	17	17	18	19
V-l	$4\text{-OCH}_3\text{-}C_6H_4$	-	14	15	17	18	-	10	14	15	16	-	16	19	20	21	-	10	14	15	21
V-m	$4\text{-CH}_3C_6H_4$	-	13	15	18	20	-	13	15	18	20	-	10	11	12	15	-	14	16	18	21

Zone of Inhibition in milli meter, 5, 25, 50,100,250 = various concentration

Comp. No.	Substituent group R	*E. COLI* MTCC 443					*P. AERUGINOSA* MTCC 424					*S. AUREUS* MTCC 96					*S. PYOGENES* MTCC 442				
		5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
V-a	$-C_6H_5$	-	15	17	18	22	-	11	14	16	19	-	15	17	20	21	-	13	15	16	20
V-b	$4\text{-Cl-}C_6H_4$	-	11	12	14	15	-	11	12	13	15	-	12	14	15	16	-	14	15	17	21
V-c	$2\text{-OH-}C_6H_4$	-	13	13	18	21	-	10	15	18	21	-	11	14	15	18	-	12	14	18	18
V-d	$4\text{-OH-}C_6H_4$	-	14	14	15	17	-	10	13	15	19	-	14	18	18	20	-	11	15	18	20
V-e	$3\text{-OH-}C_6H_4$	-	12	14	19	22	-	11	14	19	20	-	11	12	15	18	-	11	15	17	21
V-f	$4\text{-NO}_2\text{-}C_6H_4$	-	12	15	15	19	-	12	14	16	21	-	11	14	16	18	-	11	14	17	19
V-g	$3\text{-NO}_2\text{-}C_6H_4$	-	13	15	17	18	-	10	13	14	15	-	16	22	22	24	-	12	14	17	20
V-h	$4\text{-Br-}C_6H_4$	-	14	15	18	19	-	13	17	19	21	-	10	15	16	18	-	11	14	18	21
V-i	$4\text{-CH}_3\text{SO}_2\text{-}C_6H_4$	-	13	13	15	17	-	11	12	15	16	-	11	14	16	17	-	12	13	14	17
V-j	$2,4\text{diOH-}C_6H_3$	-	12	13	15	17	-	13	15	18	19	-	10	13	14	15	-	15	18	19	20
V-k	$2,4\text{-diCl-}C_6H_3$	-	14	17	19	20	-	11	16	19	22	-	10	14	16	18	-	17	17	18	19
V-l	$4\text{-OCH}_3\text{-}C_6H_4$	-	14	15	17	18	-	10	14	15	16	-	16	19	20	21	-	10	14	15	21
V-m	$4\text{-CH}_3C_6H_4$	-	13	15	18	20	-	13	15	18	20	-	10	11	12	15	-	14	16	18	21

TABLE 3: ANTIBACTERIAL ACTIVITY TABLE

Standard Drugs	*E. COLI* MTCC 443					*P. AERUGINOSA* MTCC 424					*S. AUREUS* MTCC 96					*S. PYOGENES* MTCC 442				
	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
Ampicillin	11	14	16	18	19	10	13	14	16	18	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	10	13	19	20	20	12	14	19	20	21	14	17	23	23	23	14	17	18	19	21
Ciprofloxacin	16	19	21	21	22	17	19	21	22	22	20	23	28	28	28	20	23	24	26	27
Norfloxacin	18	19	20	21	21	19	22	25	26	28	22	25	26	27	29	18	19	21	23	23

Zone of Inhibition in milli meter, 5, 25, 50,100,250 = various concentration

TABLE 4: ANTIFUNGAL ACTIVITY TABLE

Comp. No.	Substituent group R	*A. NIGER* MTCC 282					*C. ALBICANS*				
		5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
V-a	$-C_6H_5$	-	19	20	23	24	-	18	20	24	25
V-b	4-Cl-C_6H_4	-	22	22	24	24	-	18	19	22	25
V-c	2-OH-C_6H_4	-	18	21	22	24	-	18	21	25	23
V-d	4-OH-C_6H_4	-	18	19	24	22	-	18	20	24	25
V-e	3-OH-C_6H_4	-	18	20	22	24	-	19	22	25	23
V-f	4-NO_2-C_6H_4	-	18	20	21	22	-	21	22	23	25
V-g	3-NO_2-C_6H_4	-	18	19	21	22	-	22	22	24	24
V-h	4-Br-C_6H_4	-	21	21	23	24	-	19	22	25	25
V-i	4-CH_3SO_2-C_6H_4	-	18	18	19	22	-	18	18	21	22
V-j	2,4diOH-C_6H_3	-	18	18	21	22	-	18	20	22	23
V-k	2,4-diCl-C_6H_3	-	20	20	24	24	-	20	22	22	24
V-l	4-OCH_3-C_6H_4	-	19	20	21	22	-	20	22	24	25
V-m	4-$CH_3C_6H_4$	-	18	20	22	22		18	20	21	22

Zone of Inhibition in milli meter, 5, 25, 50,100,250 = various concentration

TABLE 5: ANTIFUNGAL ACTIVITY TABLE

Standard Drugs	*A. NIGER* MTCC 282					*C. ALBICANS* MTCC 227				
	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml	5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml	250 µg/ml
Greseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

Zone of Inhibition in milli meter, 5, 25, 50,100,250 = various concentration

CONCLUSION: Some of the compounds synthesized shows promising antimicrobial activity in particular, the compound v-h v-m shows promising antimicrobial activity. It is there for important to anticipate that appropriate molecular mini-pulsation of these compounds may result in the compounds with potent antimicrobial action.

However, certain structural alterations did not increase antimicrobial activity and working ahead in that direction may give quite promising results.

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REFERENCES:

1. Haskell C: Cancer Treatment, Philadelphia Saunders, 1985, 2, 43-106.
2. Http: / / www.answers.com /drug& r=67
3. Wolff ME: Bueger's .Medicinal Chemistry, New York. Wiley Inter – science. 1979.
4. Selvam P, Chandramohan M, DeClercq E, Witvrouw M and Christophe P: Synthesis and anti –HIV activity of 4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene) amino]-N (4, 6-dimethyl-2-pyrimidiny)-benzene sulfonamide and its derivatives. Eur J Pharm Sci, 2001; 14(4): 313-316.
5. La Collla, Paolo M, Stefano S: Pyrazole- Related Derivatives Endowed with Antitumor and Antiviral activities, Procedures for their preparation, Pharmaceutical formulations containing them Chem. Ber., 1885; 18 (1): 311-317.
6. Rathelot P, Azas N, Hussein E, Delmas F: 1, 3-Diphenylpyrazoles: synthesis and antiparsitic activities of azolmethine derivatives Eur J Med Chem. 2002; 37(8): 671-679.
7. Ejima A, Obsuki S: "Pyrazole Derivatives". PCT Int. Appl., (wo/1998/032739)
8. Vinod KS and Shipra S: "Synthesis and characterization of trivalent chromium, manganese, iron and cobalt complexes with Schiff bases deried from 4-amino-5-mercapto-1, 2, 4-triazoles". Indian Journal of Chemistry, Vol.-45-A, 1368-1374 (2006)

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