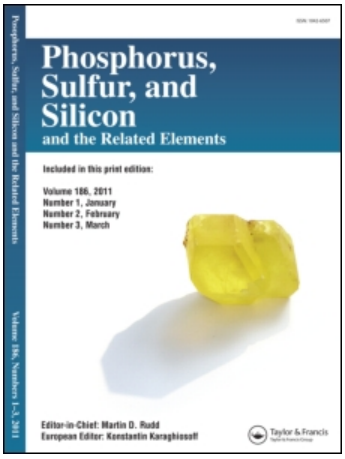

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

UTILITY OF 1-(2,4-DIMETHOXYPHENYL)-3-ARYL-PROP-2-ENE-1-ONES AS RING TRANSFORMER IN PREPARING HETEROCYCLIC COMPOUNDS AND THEIR POTENTIAL BIOLOGICAL ACTIVITIES

M. A. I. Salem[a]; E. A. Soliman[a]; M. B. Smith[b]; M. R. Mahmoud[a]; M. E. Azab[a]
[a] Ain Shams University, Abbassia, Cairo, Egypt [b] Connecticut State University, Connecticut, USA

Online publication date: 11 August 2010

To cite this Article Salem, M. A. I. , Soliman, E. A. , Smith, M. B. , Mahmoud, M. R. and Azab, M. E.(2004) 'UTILITY OF 1-(2,4-DIMETHOXYPHENYL)-3-ARYL-PROP-2-ENE-1-ONES AS RING TRANSFORMER IN PREPARING HETEROCYCLIC COMPOUNDS AND THEIR POTENTIAL BIOLOGICAL ACTIVITIES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 1, 61 — 76
To link to this Article: DOI: 10.1080/10426500490257041
URL: http://dx.doi.org/10.1080/10426500490257041

Phosphorus, Sulfur, and Silicon, 179:61–76, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490257041

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UTILITY OF 1-(2,4-DIMETHOXYPHENYL)-3-ARYL-PROP-2-ENE-1-ONES AS RING TRANSFORMER IN PREPARING HETEROCYCLIC COMPOUNDS AND THEIR POTENTIAL BIOLOGICAL ACTIVITIES

M. A. I. Salem,[a] *E. A. Soliman,*[a] *M. B. Smith,*[b]
M. R. Mahmoud,[a] *and M. E. Azab*[a]
Ain Shams University, Abbassia, Cairo, Egypt;[a] *and*
Connecticut State University, Connecticut, USA[b]

(Received May 20, 2003; accepted July 17, 2003)

*As an effort to synthesize new heterocyclic compounds, which would be expected to have a pharmacological and biological activities, we report here the reactivity of 1-(2,4-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**Ia&b**), as Michael acceptors under different conditions, towards different Michael donors namely, pyrazolin-5-one, 2-cyanomethylthiazolidin-4-one, thiobarbituric acid, cyclohexanone, and ethyl cyanoacetate affording the adducts bispyrazolo[5,4-b]-4H-pyranes **III**, 5-oxopyrazolin-4-yl-propan-1-ones **IV**, 2-(4-oxothiazolidine-2-yl)-5-oxopentano-carbonitrile **XI**, 4-oxo-4H-pyranol[2,3-d]tetrahydropyrimidin-2-thiones **XVI**, cyclohexano[b]-4H-pyran **XVII**, ethyl-5-oxo-pentanoate **XVIII**, and 1-aroyl-2-arylcyclopropanes **XIX** respectively. Fusion of **XI** with excess ammonium acetate yielded 2-aminopyridine derivative **XII** and 2-aminotetrahydropyridine derivative **XIII**. Diazotization of **XII** by treatment with HNO_2 at 0°C produced the diazonium chloride derivative **XIV** which underwent coupling reaction with phenolic compounds to yield the azo-disperse dyes **XV**. Alkaline hydrolysis of **XVIII** afforded the corresponding acid **XX** which reacted with hydrazines by fusion to yield the diazapinone derivatives **XXI**. The structures of the products obtained were confirmed by elemental analysis, infrared, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. The biological activity for some synthesized products are screened.*

Keywords: 2-Cyanomethylthiazolidin-4-one; 4-oxo-4H-pyrano[2,3-d]tetrahydropyrimidin-2-thiones; azo-disperse dyes; diazapinone pyrazolin-5-one; thiobarbituric acid

The authors would like to express their appreciation to Prof. Dr. K. P. Zeller, Institute fur Organische Chemie, Tubingen University, Tubingen, Germany for performing some ^{1}H- and ^{13}C-NMR, and mass spectra. Many thanks to Prof. Dr. Zahraa Karam El-Din, Microbiology Department, Faculty of Science, Ain Shams University for achievement of biological activities evaluation of some newly synthesized compounds.

Address correspondence to M. A. I. Salem, Synthetic Organic Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt.

Pyrazolin-5-one derivatives were found to exhibit antiinflammatory,[1,2] herbicidal,[3–6] fungicidal,[7–9] bactericidal,[7,10] and antiarthitic[1] effects, and they have been used as plant growth regulators.[6] Therefore, we attempted to prepare pyranopyrazole derivatives according to the published articles.[11,12] The reaction of chalcone **I** with pyrazolone derivatives **IIa** (R=Ph) and **IIb** (R=Me), has been previously claimed to afford the normal Michael adduct[13a] or the pyranopyrazole derivative. Herein, no pyranopyrazole could be isolated in the above reaction. Instead, we have found that the reaction products were the bis-pyrazolopyrane **III** as colorless crystals together with the Michael adduct **IV** and 2,4-dimethoxy acetophenone. Compounds **III** were allowed to react with aqueous potassium hydroxide (10%) to yield (**Va–d**) respectively. The structures of **Va–d** were found to be identical with those previously prepared.[13b]

Compound **III** has further support by identity (m.p., mixed m.p., TLC, and IR comparison) with an authentic sample resulted either from the reaction of 4-arylidene-1-phenyl-3-methylpyrazolin-5-one with **II** (1:1 molar ratio) or prepared from the reaction of **II** with suitable aromatic aldehyde (2:1 molar ratio).

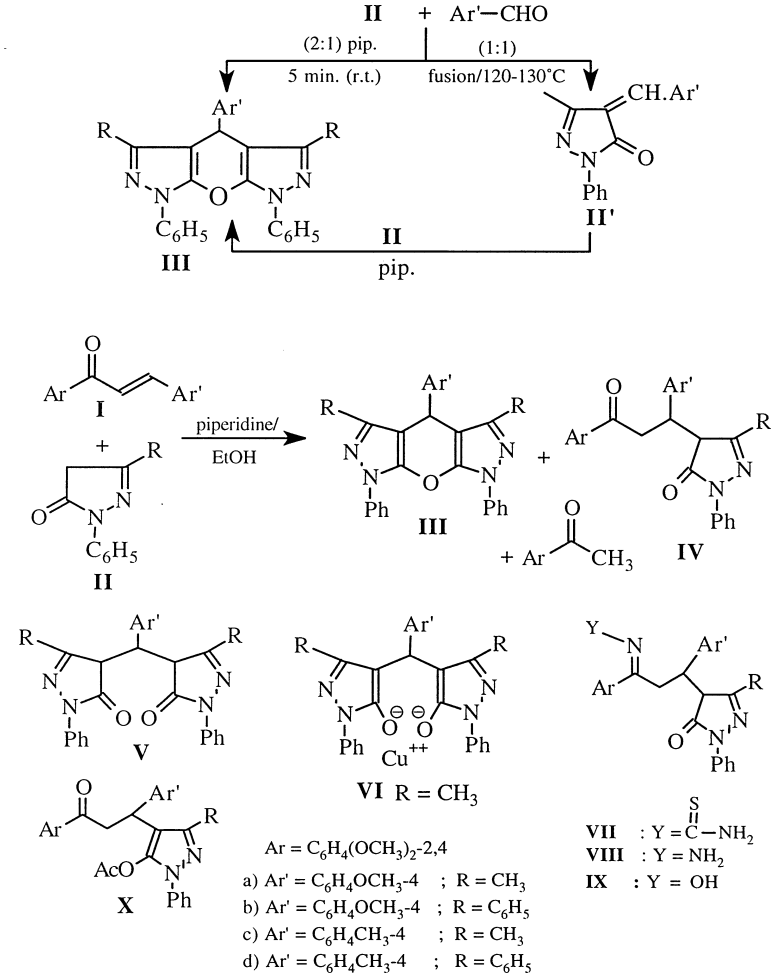
In order to obtain further information on the enolic structure of **V**, the complexation reaction of **Va&b** with Cu^{+2} was investigated.[14] To ethanolic solution of **Va&b**, copper acetate [$Cu(OAc)_2$] solution was added which rapidly formed cupric salts **VIa&b**. According to the elemental analysis of **VIa&b**, the ratio of Cu and **V** was 1:1. **IR** spectra of **VI** did not show the two characteristic bands to be strongly H-bonded enolic-OH at 2600–2500 cm^{-1} due to cooperative proton transfer[15] and around 1400 cm^{-1} as the bending vibrations of enolic =C-OH groups,[16a–c] indicating the absence of the enolic OH group (Scheme 1).

The adducts **IVb&c** were fused with thiourea in an oil-bath at 160°C and/or hydrazine hydrate (80%) in an oil-bath at 140°C to give **VIIa&b** and **VIIIa&b**, respectively.

Refluxing **IVb&c** with hydroxylamine hydrochloride in pyridine and/or with acetic anhydride (freshly distilled) for 8 h afforded the oxime **IXa&b** and the acetate **Xa&b** respectively (Scheme 1).

On the other hand, the Michael adduct (**XI**) was formed upon treatment of chalcone **Ia** with 2-cyanomethyl-thiazolidin-4-one. Treatment of **XI** with fused ammonium acetate in an oil bath at 160–170°C afforded (**XII**) and (**XIII**).[17,18] Diazotization of **XII** with $NaNO_2$/HCl produced the diazonium chloride salt **XIV** which, on coupling with phenolic compounds, afforded the azo-disperse dyes **XV**.

The reaction of chalcone with thiobarbituric has been previously reported to afford pyranopyrimidine derivatives.[19] Herein, the reaction of chalcones **Ia&b** with thiobarbituric in boiling acetic acid

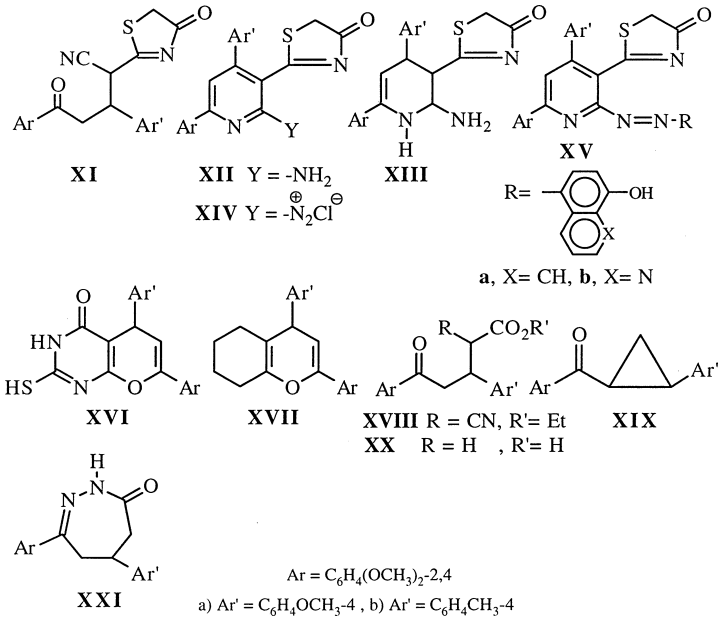


SCHEME 1

or by fusion at 130–140°C, using anhydrous zinc chloride, produced solid products which were identified to be 4-oxo-4H-pyrano[2,3-d]tetrahydropyrimidin-2-thione derivatives (**XVIa&b**).

Sammour et al.[20] reported that chalcones reacted with cyclohexanone in ethanolic sodium hydroxide solution to give the normal Michael adducts. Herein the reaction of the chalcones (**Ia&b**) with cyclohexanone afforded the Michael cyclized product[21] (**XVIIa&b**).

It has been reported that the reaction of ethyl cyanoacetate with different α,β-unsaturated ketones gave different Michael adducts according to reaction conditions.[22,23] In the present work, we reinvestigated



SCHEME 2

the base-catalyzed addition of ethyl cyanoacetate to the title compound **Ia&b** which gave the Michael adduct (**XVIIIa&b**) and the cyclopropane (**XIXa&b**).

Acid hydrolysis of **XVIIIa&b** using conc.H_2SO_4 afforded acids (**XXa&b**). Fusion of (**XXa&b**) with hydrazine hydrate furnished the diazapinone derivatives (**XXIa&b**) (Scheme 2).

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were recorded on mattson 1000 F.T.I.R. spectrometer and 283 Perkin-Elmer spectrophotometer using KBr as a wafer technique. The ^{1}H-NMR spectra and ^{13}C-NMR were determined on Bruker AC 270 and Bruker AC 250(200 MHz). In all ^{1}H-NMR and ^{13}C-NMR experiments, the internal standard was TMS (in δ-scale). All chemical shifts were downfield from TMS.

The G.C. mass spectra were determined on AEI MS-902 mass spectrometer. Mass spectra were determined on MS-TSQ 70 Finnigan MAT.

Reaction of Ia&b with 1-Phenyl-3-substitutedpyrazolin-5-one (IIa,b); Formation of 4-Aryl-bis-1-phenyl-3-substitutedpyrazolo[5,4-b]-4H-pyran (IIIa–d) and 3-Aryl-1-(2,4-dimethoxyphenyl)-3-(1-phenyl-3-substituted-5-oxopyrazolin-4-yl)-propan-1-one (IVa–d)

A mixture of chalcones[20,24] **Ia** or **Ib** (0.01 mmol in 20 mL ethanol) and pyrazolones **IIa** or **IIb** (0.012 mmol, in 20 mL ethanol) was refluxed, in the presence of 2 mL piperidine, for 6 h. A white solid, which was formed on hot, was filtered off and recrystallized from acetic acid giving **IIIa–d** respectively. Slow evaporation of the filtrate produced another white crystals, which was recrystallized from ethanol yielding the adducts **IVa–d** respectively (c.f. Table I).

Compounds **IIIa–d** were prepared authentically by two methods. *Method A*: via a one step reaction by reacting **IIa** or **IIb** with *p*-anisaldehyde or *p*-tolualdehyde (2:1 molar ratio) in the presence of a few drops of piperidine. After stirring for 5 min at room temperature, the precipitates are obtained. *Method B*: via a two step reaction, by fusion of **IIa** or **IIb** with *p*-anisaldehyde or *p*-tolualdehyde (1:1 molar ratio) at 120–130°C for 2 h to give the 4-arylidene derivatives which on treatment with another mole of **IIa&b** in ethanol, in the presence of a few drops of piperidine, and refluxing for 4 h gave **IIIa–d**.

^{1}H NMR spectrum of **IIIa** (DMSO-d_6) δ at 8.2 (d,d, 4H, *p*-substituted phenyl ring protons), at 7.5–6.9 (m, 10H, two phenyl ring protons), at 5.8 (s, 1H, C_4-H pyran), at 3.3 (s, 3H, *p*-methoxy protons) and at 2.2 (s, 6H, the two methyl protons); **^{1}H NMR** of **IIIc** (DMSO-d_6) shows δ at 7.9–7.7 (d, d, 4H, aromatic protons of the *p*-substituted phenyl ring), at 7.3-6.9 (m, 10H, aromatic protons of the phenyl groups), at 5.6 (s, 1H, C_4-H pyran), at 2.3 (s, 6H, two methyl protons of the pyrazole rings) and at 2.1 (s, 3H, methyl protons of the tolyl ring); **MS**, m/e (%) 432 [$M^{+\cdot}$] (2.3%), 276 (100%), 248 (20.1%), 185 (44.5%), 174 (7.8%), 156 (7.4%), 144 (12.1%), 134 (24.4%), 132 (17.4%), 118 (18.0%), 106 (4.1%), 105 (10.3%), 92 (5.6%), 91 (2.5%), 77 (17.7%), 65 (7.1%); **^{1}H NMR** of **IIId** (DMSO-d_6) shows signals at 8.2–8.0 (d,d 4H, aromatic protons of the *p*-substituted phenyl ring), at 7.4–7.0 (m, 20H, aromatic protons four phenyl groups), at 5.85 (s, 1H, C_4-H pyran) and at 2.2 (s, 3H, methyl protons); **MS** m/e (%) 556 [$M^{+\cdot}$] (3.3%), 396 (100%), 368 (22.6%), 285 (42.3%), 218 (6.1%), 194 (14.9%), 182 (11.2%), 134 (26.0%), 121 (12.2%), 117 (19.2%), 106 (4.4%), 91 (6.1%), 77 (18.5%) and 65(8.8%). IR data are shown in Table II.

^{1}H NMR of **IVb** (DMSO-d_6) δ at 8.1 (d, 2H, J = 9.1 Hz, o-H's in p-methoxy-phenyl ring), 7.5–6.8 (m, 15H, aromatic protons), 4.1 (d, 1H, J = 8.6 Hz, C_4-H pyrazolone), 3.25 (s, 3H, OMe), 3.4 (s, 6H, 2 OMe), at 2.9 (m, 1H, benzylic proton) and at 2.5 (d, 2H, J = 11.0 Hz, -CH_2CO). **MS**,

TABLE I Physical Data of Newly Synthesized Products

Compd.	m.p. °C/(color)	Solvent yield (%)	M.F./(m. wt)	Analysis Calcd. Found C%	H%	N%	Cu%
IIIa	212–214	AcOH	$C_{28}H_{24}N_4O_2$	74.98	5.39	12.49	
	(white)	(46)	(448)	74.82	5.17	12.30	
IIIb	217–219	AcOH	$C_{38}H_{28}N_4O_2$	79.70	4.93	9.78	
	(white)	(43)	(572)	79.53	4.75	9.59	
IIIc	214–216	AcOH	$C_{28}H_{24}N_4O$	77.75	5.59	12.95	
	(white)	(43)	(432)	77.62	5.50	12.80	
IIId	221–223	AcOH	$C_{38}H_{28}N_4O$	81.99	5.07	10.06	
	(white)	(41)	(556)	81.90	4.92	9.88	
IVa	124–126	L.P. 80–100°C	$C_{28}H_{28}N_2O_5$	71.19	5.93	5.93	
	(white)	(40)	(472)	71.02	5.81	5.79	
IVb	102–104	L.P. 80-100°C	$C_{33}H_{30}N_2O_5$	74.16	5.62	5.24	
	(white)	(38)	(534)	73.98	5.44	5.05	
IVc	127–129	L.P. 80-100°C	$C_{28}H_{28}N_2O_4$	73.68	6.14	6.14	
	(white)	(38)	(456)	73.49	6.03	5.95	
IVd	113–115	L.P. 80-100°C	$C_{33}H_{30}N_2O_4$	76.45	5.79	5.41	
	(white)	(37)	(518)	76.28	5.61	5.23	
Va	171–173	EtOH	$C_{28}H_{26}N_4O_3$	72.09	5.62	12.01	
	(Orange)	(85)	(466)	71.93	5.43	11.85	
Vb	176–178	EtOH	$C_{38}H_{30}N_4O_3$	77.27	5.12	9.49	
	(Orange)	(82)	(590)	77.11	4.91	9.30	
Vc	164–166	EtOH	$C_{28}H_{26}N_4O_2$	74.65	5.82	12.44	
	(Light red)	(78)	(450)	74.49	5.70	12.27	
Vd	172–174	EtOH	$C_{38}H_{30}N_4O_2$	79.42	5.26	9.75	
	(Light red)	(74)	(574)	79.25	5.11	9.58	
VIa	>360	—	$C_{28}H_{24}N_4O_3Cu$	63.69	4.58	10.61	12.03
	(Brown)	(88)	(527.5)	63.49	4.41	10.44	12.21
VIb	>360	—	$C_{28}H_{24}N_4O_2Cu$	65.68	4.72	10.94	12.41
	(Brown)	(91)	(512)	65.51	4.61	10.84	12.51
VIIa	196–198	EtOH	$C_{34}H_{32}N_4O_4S$	68.90	5.44	9.45	
	(Yellow)	(41)	(592)	68.79	5.40	9.51	
VIIb	191–193	EtOH	$C_{29}H_{30}N_4O_3S$	67.68	5.88	10.89	
	(Yellow)	(40)	(514)	67.74	5.70	10.98	
VIIIa	167–169	EtOH	$C_{33}H_{32}N_4O_4$	72.24	5.88	10.21	
	(Orange)	(41)	(548)	72.46	6.09	10.27	
VIIIb	163–165	EtOH	$C_{28}H_{30}N_4O_3$	71.47	6.43	11.91	
	(Orange)	(41)	(470)	71.57	6.44	12.01	
IXa	181–183	Benzene	$C_{33}H_{31}N_3O_5$	72.11	5.69	7.65	
	(Pale Yellow)	(53)	(549)	71.91	5.46	7.87	
IXb	180–182	Benzene	$C_{28}H_{29}N_3O_4$	71.32	6.20	8.91	
	(Pale Yellow)	(49)	(471)	71.40	6.15	8.76	
Xa	55–57	L.P-B	$C_{35}H_{32}N_2O_6$	72.90	5.59	4.86	
	(Orange)	(65)	(576)	72.77	5.48	4.68	
Xb	52–54	L.P-B	$C_{30}H_{30}N_2O_5$	72.27	6.06	5.62	
	(Orange)	(61)	(498)	72.06	5.90	5.41	

(*Continued on next page*)

TABLE I Physical Data of Newly Synthesized Products (*Continued*)

Compd.	m.p. °C/(color)	Solvent yield (%)	M.F./(m.wt)	Analysis Calcd. Found C%	H%	N%	Cu%
XI	285-288	aq.EtOH	$C_{23}H_{22}N_2O_5S$	63.00	5.06	6.39	
	(Deep brown)	(59)	(438)	63.14	5.14	6.28	
XII	180-183	AcOH	$C_{23}H_{21}N_3O_4S$	63.43	4.86	9.65	
	(Riddish brown)	(49)	(435)	63.26	4.77	9.47	
XIII	147-150	EtOH	$C_{23}H_{25}N_3O_4S$	62.85	5.73	9.56	
	(Yellow)	(41)	(439)	62.69	5.51	9.38	
XVa	224-226	EtOH	$C_{33}H_{26}N_4O_5S$	67.10	4.44	9.49	
	(Reddish brown)	(74)	(590)	66.93	4.56	9.67	
XVb	191-193	EtOH	$C_{32}H_{25}N_5O_5S$	64.97	4.23	11.84	
	(Reddish brown)	(78)	(591)	65.08	4.12	12.00	
XVIa	316-318	AcOH	$C_{22}H_{20}N_2O_5S$	62.26	4.75	6.60	
	(Red)	(89)	(424)	62.09	4.60	6.41	
XVIb	313-315	AcOH	$C_{22}H_{20}N_2O_4S$	64.69	4.94	6.86	
	(Reddish-brown)	(87)	(408)	64.53	4.78	6.79	
XVIIa	111-113	EtOH	$C_{24}H_{26}O_4$	76.17	6.92	—	
	(white)	(41)	(378)	75.95	6.74	—	
XVIIb	105-107	EtOH	$C_{24}H_{26}O_3$	79.53	7.23	—	
	(white)	(40)	(362)	79.39	7.17	—	
XIXa	133-135	Ethanol	$C_{19}H_{20}O_4$	73.06	6.45	—	
	(white)	(9)	(312)	72.96	6.35	—	
XIXb	127-129	Ethanol	$C_{19}H_{20}O_3$	77.00	6.80	—	
	(white)	(8)	(296)	76.91	6.69	—	
XXa	271-273	Benzene	$C_{20}H_{22}O_6$	67.03	6.19	—	
	(Buff)	(67)	(358)	67.12	6.01	—	
XXb	282-284	Benzene	$C_{20}H_{22}O_5$	70.16	6.48	—	
	(Buff)	(63)	(342)	69.98	6.67	—	
XXIa	148-150	EtOH	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90	
	(white)	(42)	(354)	67.67	6.09	7.72	
XXIb	140-142	EtOH	$C_{20}H_{22}N_2O_3$	70.99	6.55	8.28	
	(white)	(38)	(338)	70.84	6.40	8.20	

m/e (%) 534 [$M^{+\cdot}$] (4.5%), 354 (11.1%), 298 (88.0%), 283 (39.1%), 236 (100%), 165 (17.1%), 132 (2.7%), 131 (19.6%), 103 (2.4%), 101 (2.0%), 91 (13.6%), 77 (2.7%), 65 (2.0%); **^{13}C NMR** is shown in Figure 1.

^{1}H NMR of **IVc** (DMSO-d_6) δ at 8.2–6.7 (m, 12H, arom. H's,) 4.2 (d, 1H, J = 8.7 Hz, C_4-H pyrazolone), 3.9 (s, 6H, 2 OMe), 3.1 (m, 1H, benzylic proton), 2.7 (d, 2H, J = 11.0 Hz, CH_2CO) and at 2.4 (s, 6H, two methyl protons).

^{1}H NMR of **IVd** (DMSO-d_6) δ at 8.1–7.1 (m, 17H, arom. H's), 4.1 (d, 1H, J = 9.2 Hz, C_4-H pyrazolone), 3.9–3.8 (two s, 6H, 2 OMe), 3.2 (m, 1H, benzylic proton), 2.8 (d, 2H, J = 11.1 Hz, CH_2CO) and at 2.3 (br, s, 3H, Me-Ar); **MS**, m/e (%) 282[M-236](17.1%), 236(69.4%), 165(100%), 150(14.6%), 131(2.2%), 122(12.2%), 116(1.1%), 103(26.3%), 91(24.5%), 77(17.8%).

TABLE II IR Data of the Newly Synthesized Products

Compd.	$\nu_{C=C}$	$\nu_{C=N}$	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (pyrazolone) /$\nu_{C\equiv N}$	$\nu_{CH(aliph.)}$	$\nu_{CH(arom.)}$	ν_{NH}/ν_{OH}
IIIa	1605	1620	—	—	2980, 2880, 2720	3060	—
IIIb	1600	1615	—	—	2960, 2870, 2725	3040	—
IIIc	1595	1620	—	—	2950, 2860, 2710	3035	—
IIId	1605	1615	—	—	2970, 2865, 2710	3050	—
IVa	1605	1620	1660	1715	2945, 2860	3080	3440
IVb	1610	1620	1670	1720	2980, 2870	3070	3450
IVc	1605	1615	1660	1720	2930, 2850	3065	3460
IVd	1600	1610	1660	1725	2945, 2860	3080	3460
Va	1595	1615	—	1715	2940, 2850	3055	3450
Vb	1605	1620	—	1720	2970, 2880	3065	3445
Vc	1610	1620	—	1720	2965, 2875	3060	3460
Vd	1605	1615	—	1725	2975, 2880	3070	3455
VIa	1595	1605	—	—	2960, 2835	3080	—
VIb	1570	1610	—	—	2970, 2845	3065	—
VIIa	1605	1630	—	1720	2930, 2865	3085	3455
VIIb	1595	1620	—	1710	2920, 2855	3060	3430
VIIIa	1605	1615	—	1710	2960, 2850	3065	3450
VIIIb	1600	1610	—	1725	2935, 2860	3010	3380
IXa	1605	1620	—	1720	2950, 2860	3030	3450
IXb	1600	1615	—	1715	2930, 2850	3020	3430
Xa	1600	1615	1655 aroyl, 1700 acetyl	—	2980, 2855	3060	—
Xb	1600	1610	1655 aroyl, 1700 acetyl	—	2965, 2845	3070	—
XI	1600	1610	1640,1665	2245	2990, 2850	3040	—
XII	1595	1615	1670	—	2970, 2850	3030	3460-3480 (br.)
XIII	1600	1615	1670	—	2980, 2860	3040	3460-3470 (br.)
XVa	1590	1615	1665	—	2970,2855	3030	3450
XVb	1590	1615	1660		2975, 2865	3035	3455
XVIa	1605	1610	1665, 1185 $\nu_{C=S}$	—	2930, 2860	3075	3450-3480 (br.)
XVIb	1600	1615	1655, 1180 $\nu_{C=S}$	—	2925, 2855	3070	3445-3480 (br.)
XVIIa	1610		—	—	2960, 2910 2860	3080	—
XVIIb	1610		—	—	2965, 2910 2850	3070	—
XVIIIa	1600		1735, 1670	2240	2980, 2840	3035	3500
XVIIIb	1605		1730, 1660	2230	2960, 2835	3015	3450
XIXa	1600		1660	—	2975, 2935 2900, 2840	3020	—
XIXb	1600	1620	1650	—	2970, 2930 2900, 2850	3015	—
XXa	1605	—	1670 aroyl, 1710 acid	—	2945, 2850	3045	3550 (br.)

(*Continued on next page*)

TABLE II IR Data of the Newly Synthesized Products (*Continued*)

Compd.	$\nu_{C=C}$	$\nu_{C=N}$	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (pyrazolone) /$\nu_{C=N}$	$\nu_{CH(aliph.)}$	$\nu_{CH(arom.)}$	ν_{NH}/ν_{OH}
XXb	1610	—	1665 aroyl, 1705 acid	—	2935, 2840	3045	3500 (br.)
XXIa	1600	1620	1660	—	2990, 2940 2890,2825	3040	3445-3480 (br.)
XXIb	1605	1625	1660	—	2980, 2940 2880,2825	3030	3440-3490 (br.)

Reaction of III with Aqueous Potassium Hydroxide (10%); Formation of bis-(1-Phenyl-3-substituted-5-oxopyrazolin-4-yl) Aryl Methanes (Va-d)

To (0.01 mmol) of **IIIa–d**, 40 mL aqueous alcoholic solution of potassium hydroxide (10%) was added, the reaction mixture was refluxed for 6 h followed by concentrating the solution then pouring over ice/HCl mixture, an orange solid was precipitated, which was filtered off, dried, and recrystallized from ethanol giving the adducts **Va–d** respectively.

Some of the adducts **IIIa–d** were previously prepared by other methodology.[13b]

Reaction of Va&c with Cupric Acetate; Formation of Copper Salt VIa&b

A solution of cupric acetate monohydrate (0.05 mmol) in ethanol (15 mL) was added dropwise into ethanolic solution (15 ml) containing **Va** or **Vc** (0.01 mmol) with stirring. A brown precipitate was formed immediately. After additional stirring for 0.5 h, the precipitate was separated by centrifugation, washed with ethanol (95%) and water several times then again with (95%) ethanol and then dried affording the copper salts **VIa&b**.

Reaction of IVb&c with Thiourea and/or Hydrazine Hydrate; Formation of N-thiocarbamido-3-aryl-1-(2,4-dimethoxyphenyl)-3-(1-phenyl-3-substituted-5-oxo-pyrazolin-4-yl)propan-1-one Imine (VIIa,b) and 3-Aryl-1-(2,4-dimethoxyphenyl)-3-(1-phenyl-3-substituted-5-oxopyrazolin-4-yl)propan-1-one hydrazones (VIIIa,b)

A mixture of **IVb** or **IVc** (0.01 mmol) was heated with thiourea (0.015 mmol, 1.05 g) and/or hydrazine hydrate (80%) (0.015 mmol, 0.75 g) at 140°C for 6 h. The reaction mixture was triturated with

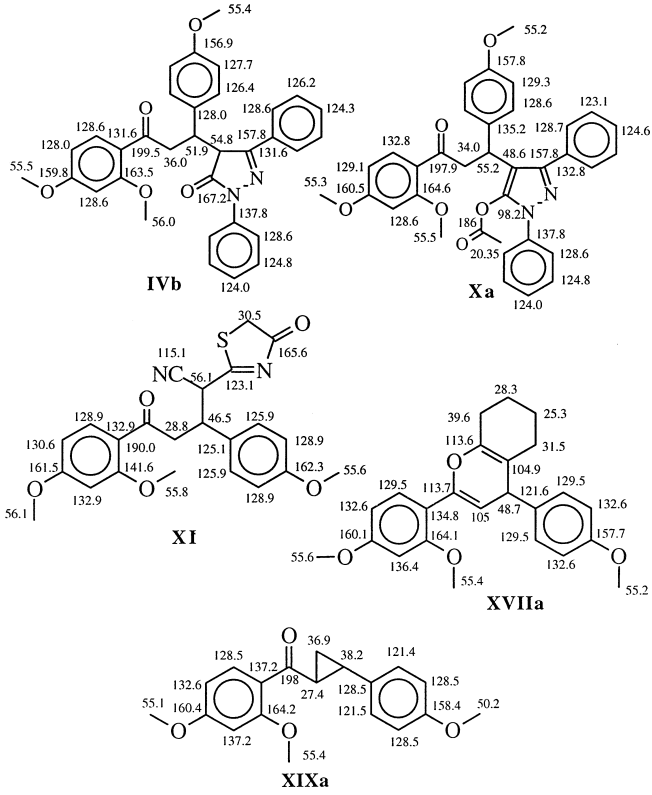


FIGURE 1

water and dilute HCl. The crude product was spread over silica gel using ethylacetate-light petrol 60–80°C (2:8) as an eluent to separate the desired adduct using TLC preparative technique, dissolving the spots in ethylacetate followed by slow evaporation gave an oil product which on trituration with drops of methanol gave the solid products **VIIa&b** and **VIIIa&b** respectively.

Reaction of IVb&c with Hydroxylamine Hydrocloride; Formation of 3-Aryl-1-(2,4-dimethoxyphenyl)-3-(1-phenyl-3-substituted-5-oxopyrozolin-4-yl)propan-1-one oximes (IXa&b)

A mixture **IVb** or **IVc** (0.01 mmol) and hydroxylamine hydrochloride (0.015 mmol, 1.05 g) was refluxed in pyridine (15 mL) for 6 h. The

reaction mixture was poured over ice and HCl, a pale yellow solid was separated out, filtered off, washed with H_2O several times, dried, and recrystallized from the proper solvent affording the corresponding oximes **IXa&b** respectively.

^{1}H NMR of **IXa** ($CDCl_3$) exhibited the following signals at δ 11.4 (s, 1H, =N—OH), 8.3 (d, 2H, J = 9.1 Hz, o-H's in p-methoxyphenyl ring), 7.8-6.8 (m, 15H, aromatic protons), 4.2 (d, 1H, J = 8.6 Hz, C_4-H pyrazolone), 3.3 (s, 3H, OMe), 3.5 (s, 6H, 2 OMe), at 2.9 (m, 1H, benzylic proton) and at 2.5 (d, 2H, J = 11.0 Hz, —CH_2CO).

Reaction of IVb&c with Acetic Anhydride; Formation of 3-(5-Acetoxy-1-phenyl-3-substituted-5-oxopyrazolin-4-yl)-3-aryl-1-(2,4-dimethoxyphenyl)propan-1-ones (Xa&b)

A solution of the products **IVb** or **IVc** (0.01 mmol) in acetic anhydride (20 ml) was refluxed for 8 h. The reaction mixture was concentrated to its half volume then poured over ice/water, an orange solid was deposited out which was recrystallized from the proper solvent yielding the products **Xa&b** respectively.

^{1}H NMR spectrum of **Xa** ($CDCl_3$) exhibits the following signals at δ (ppm):- 7.7-6.4 (m, 17H, arom. H's), 4.4 (t, 1H, CHAr′), 3.9 (s, 3H, OMe) 3.8-3.7 (two s, 6H, 2 OMe), 2.8 (d, 2H, J = 11.4 Hz, CH_2CO), and 2.0 (s, 3H, Me-CO); **MS** m/e (%) 354[M-222](21.2%), 298(88.0%), 279(6.8%), 247(5.5%), 236(100%), 180(3.9%), 165(17.6%), 150(3.1%), 135(17.6%), 132(2.1%), 131(10.0%), 121(38.5%), 102(8.2%), 91(4.2%), and 77(2.1%); **^{13}C NMR** is shown in Fig. 1.

Reaction of Chalcone Ia with 2-Cyanomethylthiazolidin-4-one; Formation of 5-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-2-(4-oxothiazolidin-2-yl)-5-oxopentano-carbonitrile (XI)

2-Cyanomethyl thiazolidin-4-one (0.01 mmol, 1.4 g) in 20 mL ethanol and sodium ethoxide (1 g sodium in 30 mL absolute ethanol) was added dropwise to an alcoholic solution of chalcone **Ia** (0.01 mmol 2.98 g) in 20 mL ethanol with stirring at room temperature for 30 min, then the reaction mixture was refluxed for 12 h, left to cool then neutralized by ice/HCl. The solid that precipitated out was filtered off, washed with water several times, then recrystallized from aq. ethanol to produce the adduct **XI**.

^{1}H NMR spectrum of **XI** (acetone-d_6) shows from low to high field signals at δ 8.5-7.9 (m, 7H, aromatic), 4.3 (d, 1H, J = 9.3 Hz, -CH-CN), 3.7 (s, 2H, S-CH_2CO-), 3.4 (s, 9H, 3 OMe), 3.0-2.8-(m, 1H, benzylic proton) and at 2.7 (d, 2H, J = 10.6 Hz, Ar-CO-CH2-); **MS** m/e (%) 438[$M^{+\cdot}$] (1.0%),

298(58.3%), 283(36.7%), 272(2.1%), 270(30.9%), 255(9.9%). 165(77.7%), 141(3.1%), 135(25.8%) 121(100%) 107(10.6%), and 92(10.2%); **^{13}C NMR** is shown in Figure 1.

Reaction of XI with Ammonium Acetate; Formation of 2-Amino-6-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-3-(4-oxothiazolidin-2-yl)pyridine (XII) and 2-Amino-6-(2,4-dimethoxyphenyl)-4-(4-methoxypenyl)-3-(4-oxothiazolidin-2-yl)tetrahydropyridine (XIII)

On an oil bath, the product **X** (0.0025 mmol 1.1 g) and 2 g of ammonium acetate were fused at 170°C for 4 h. The reaction mixture was poured over cold water then the solid formed was filtered off and washed with water several times. Fractional crystallization of the solid product afforded compounds **XII** and **XIII** respectively.

^{1}H NMR spectrum of **XII** ($CDCl_3$) exhibits the following signals at δ (ppm):- 8.4-7.6 (m, 8H, arom. H's), 4.7 (s, 2H, CH_2 of azathiazole ring), 3.7 (s, 9H, 3 OMe), and 3.3 (s, 2H, NH_2).

Diazotisation and Coupling of (XII) with Phenolic Compounds; Formation of Azodisperse Dyes (XV)

A solution of the diazonium chloride (**XIV**), prepared by diazotizing 10 mmol of **XII** in hydrochloric acid (6 mL, 6 M) with sodium nitrite (0.7 g, 10 mmol) in 10 mL water, was stirred for 30 min with cooling in ice bath to 0–5°C.

To the solution of phenolic compounds, namely, α-naphthol and/or 8-hydroxy-quinoline (1.44 g, 10 mmol) in ethanol 3 ml and 10 mmol of NaOH (6 mL, 6 M) was added dropwise while cooling at 0°C to an aqueous cold solution of the diazonium chloride **XIV** in an ice bath with continuous stirring for additional 15 min, followed by acidification with aq. HCl (50 mL, 1 M) then the solid formed was filtered off and washed with water, dried and recrystallized from the proper solvent, to give the reddish brown azo-disperse dyes (**XVa&b**) respectively.

^{1}H NMR spectrum of **XVa** ($CDCl_3$) exhibits the following signals at δ (ppm):- 10.4 (s, lH, OH), 8.3-7.6 (m, 14H, arom. H's), 4.8 (s, 2H, CH_2 of azathiazole ring), and 3.7 (s, 9H, 3 OMe).

Reaction of Chalcones Ia&b with Thiobarbituric Acid; Formation of 5-Aryl-7-(2,4-dimethoxyphenyl)-4-oxo-4H-pyrano[2,3-d]tetrahydropyrimidin-2-thione (XVIa&b)

Method A: A mixture of chalcones **Ia** or **Ib** (0.01 mmol) and thiobarbituric acid (0.12 mmol 1.72 g) was refluxed in 30 mL glacial acetic for 6 h.

A precipitate was obtained during the reflux which was filtered off and recrystallized from the proper solvent producing the products **XVIa&b** respectively.

Method B: The same reaction was repeated by fusion at 140–150°C in the presence of anhydrous $ZnCl_2$ (2 g) for 1 h. The same products **XVIa&b** were obtained after pouring over hot water and washing by water several times.

^{1}H NMR spectrum of **XVIa** (acetone-d_6) showed the characteristic signals for two NH of thiobarbituric moiety at δ 12.3 and 12.4, at 8.4-7.0 (m, 7H, aromatic and olefinic protons), at 6.3 (d, 1H, J = 14.0 Hz, olefinic proton), at 5.1 (d, lH, J = 10.8 Hz, C_4-H pyran) and at 3.9 and 3.4 (s, 9H, three methoxy protons); **MS** m/e (%) 262 [M-162$^{+\cdot}$](100%), 247(58.3%), 283(12.0%), 231(30.0%), 202(22.0%), 188(2.5%), 164(46.5%), 162(16.7%), 160(33.0%), 145(18.0%), 117(27.0%), 89(28.0%) and 63(6.0%).

Reaction of Chalcones Ia&b with Cyclohexanone; Formation of 4-Aryl-2-(2,4-dimethoxyphenyl)-cyclohexano[b]-4H-pyran (XVIIa&b)

Cyclohexanone (0.012 mmol, 1.2 mL) was added dropwise to sodium ethoxide (1 g 30 mL ethanol), then chalcones **Ia** or **Ib** (0.01 mmol), in 30 mL ethanol, was added dropwise with stirring at room temperature for 30 min, then the stirred mixture was warmed on water bath at 40–60°C for 12 h, the reaction mixture was concentrated and neutralized by ice/HCl, the solid obtained was filtered off, dried, then recrystallized from the proper solvent affording the products **XVIIa&b** respectively.

^{1}H NMR spectrum of **XVIIa** ($CDCl_3$) displayed signals at δ 8.1-7.2 (m, 7H, aromatic H), 6.3 (d, 1H, J = 14.0 Hz, olefinic H), 4.9 (d, 1H, J = 11.2 Hz, C_4-H pyran), 3.8 (s, 9H, 3 OMe) and 2.65-1.1 (m, 8H, cyclohexyl protons), **MS** m/e (%) 378[M$^{+\cdot}$](8.6%), 299(37.1%), 165(100%), 135(3.0%), 134(2.0%), 121(17.0%), 107(7.1%), 80(2.1%), 77(9.0%) and 65(5.1%); **^{13}C NMR** is shown in Figure 1.

Reaction of Chalcones Ia&b with Ethyl Cyanoacetate; Formation of Ethyl 3-Aryl-2-cyano-5-(2,4-dimethoxyphenyl)-5-oxopentanoate (XVIIIa&b) and 2-Aryl-1-(2,4-dimethoxybenzoyl)cyclopropane (XIXa&b)

Ethyl cyanoacetate (0.012 mmol, 1.3 mL) was added to a stirred solution of sodium ethoxide (1 g of Na in 20 mL of absolute ethanol), then a solution of chalcones **Ia** or **Ib** (0.01 mmol, in 20 mL absolute

ethanol) was added dropwise within 1 min. The reaction mixture was stirred and heated under reflux on water bath for 4 h. The solution was concentrated, then poured over ice/dil. HCl mixture affording a brown oil. Extraction with ether and drying over anhydrous $MgSO_4$, produced a pale brown oil. Trituration of the oil with methanol gave **XVIIIa&b** as pale yellow oil (R_f 0.63) in 40–45% yield and **XIXa&b** as white solid respectively.

^{1}H NMR spectrum of **XIXa** ($CDCl_3$, δ ppm) displayed the following signals:- at 7.7–6.4 (m, 7H, aromatic protons), at 3,9–3.7 (s, 9H, 3 OMe) and Ar-CO-CH, CH-Ar' at 3.27 , $-CH_2-$ at 1.8 due to vicinal and geminal coupling; **MS** of **XIXa** m/e (%) 312[$M^{+\cdot}$] (2.1%), 298(72.8%), 283(2.5%), 251(2.9%), 180(8.8%), 165 (100%), 137(2.2%), 135(72.9%), 121(4.2%), 107(2.4%) and 77(9.0%); **^{13}C NMR** is shown in Figure 1.

Hydrolysis of XVIIIa&b; Formation of 3-Aryl-5-(2,4-dimethoxyphenyl)-5-oxo-pentanoic Acid (XXa&b)

2 g of **XVIIIa** or **XVIIIb** was dissolved in 40 mL conc. H_2SO_4 (60%) was stirred at room temperature for 1 h. The reaction mixture was heated on steam bath for 6 h. with continuous stirring and allowed to cool to room temperature then poured into ice/water and kept overnight. The solid product that separated out was filtered off and crystallized from the proper solvent to give the acids (**XXa&b**).

^{1}H NMR spectrum of **XXa** ($CDCl_3$) exhibits the following signals at δ (ppm):- 2.9 (d, 2H, $COCH_2$, J = 11.2), 3.8 (s, 9H, 3 OMe), 4.2 (d, 2H, CH_2COOH, J = 9.4), 5.9 (m, 1H, benzylic H), 8.6–7.4 (m, 7H, aromatic H's) and 11.1 (s, 1H, COOH).

Reaction of the Acids (XXa&b) with Hydrazine Hydrate; Formation of Diazipenones (XXIa&b)

A solution of (**XXa** or **XXb**) (0.01 mmol in 40 ml n-butanol) was stirred at room temperature for 15 min until all the solid was dissolved then 0.015 mmol (0.7 ml) of hydrazine hydrate (80%) was added dropwise to the above solution with continuous for another 15 min. The reaction mixture was heated for 4 h concentrated by filtration and crystallized from suitable solvent to give diazipenone derivatives **XXIa&b** respectively.

^{1}H NMR spectrum of **XXIa** ($CDCl_3$) exhibits the following singnals at δ (ppm):- 3.1 (d, 2H, C4, J = 7.8), 3.7 (s, 9H, 3 OMe), 4.3 (d, 2H, C6, J = 11.3), 5.8 (m, 1H, C5), 7.1–8.3 (m, 7H, aromatic protons), and 9.2 (s, 1H, NH).

TABLE III Biological Activity of Some Compounds

	Inhibition							
	Aspergillus		Candida		E. coli		St. aur	
Compd.	A*	MIC	A*	MIC	A*	MIC	A*	MIC
IIIa	—	—	—	—	+	128	+	128
IIIc	—	—	—	—	—	—	—	—
IVa	—	—	—	—	+	128	+	128
IVc	—	—	—	—	+	128	+	128
Va	++	64	+	128	+++	32	+++	32
Vb	++	64	++	64	+	128	+	128
VIIa	+++	32	+++	32	++	64	++	64
VIIIa	—	—	—	—	—	—	—	—
IXa	++	64	++	64	+	128	+	128
XIIa	++	64	++	64	++	64	++	64
XIIb	++	64	—	—	+	128	+	128
XVIa	+++	32	+++	32	+++	32	+++	32
XVIb	+++	32	++	64	+++	32	++	64
VVIIIa	—	—	—	—	—	—	—	—
XXa	++	64	++	64	+++	32	+++	32
XXIa	—	—	—	—	+	128	+	128

The width of the zone of inhibition indicates the potency of antibacterial activity; (−) no antibacterial activity; (+) mild activity with the diameter of the zones equal to 0.6–0.8 cm; (++) moderate activity with the diameter of the zones equal to 1.2–1.3 cm; (+ + +) marked activity with the diameter of the zones equal to 1.8–2.0 cm. *E. coli* is Gram-negative and *St. aur* is a gram-positive bacteria and *Asperigllus flavus* and *Candida albicans* as fungi.[25–27]

CONCLUSION

From Table III it can be seen that compounds **Va**, **XVIa**, and **XXa** were the most effective against both gram-negative and gram-positive bacterial strains whereas some other compounds have moderate effect on the tested bacteria, while compounds **VIIa** and **XVIa** were the most effective against the tested fungi. We can conclude that compounds **Va**, **XVIa**, and **XXa** can be used as antibacterial agents both gram-negative and gram-positive bacteria, while compounds **VIIa** and **XVIa** can be used as antifungi agents against *Asperigllus flavus* and *Candida albicans*.

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