ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 12, pp. 2406–2412. © Pleiades Publishing, Ltd., 2013.

Synthesis, Characterization, Anti-Fungi and Anti-Bacterial Activity of New [(2-Pyridyl)-3-isatin]-bishydrazone[1]

Mostafa K. Rabia, Ahmad Desoky M. Mohamad, Nabawia M. Ismail, and Ali Abdo Mahmoud

Chemistry Department, Faculty of Science, Sohag University, 82534 Sohag, Egypt
e-mail: alyabdo8081@yahoo.com; aliabdo@science.sohag.edu.eg

Received September 2, 2013

Abstract—New [(pyridine-2-carboxaldhyde)-3-isatin]-bishydrazone (cpish), [(2-acetylpyridine)-3-isatin]-bishydrazone (apish), and [(2-benzoyl pyridine)-3-isatin]-bishydrazone (bpish) have been synthesized and characterized by the elemental analysis, IR, NMR and electronic spectra. The bioefficiency of the [(2-pyridyl)-3-isatin]-bishydrazones have been examined for their in-vitro antibacterial and antifungal activity against many types of bacteria and fungal cultures which are common contaminants of the environment in Egypt and some of which are involved in human and animal diseases or in plant diseases or frequently reported from contaminated soil, water, and food substances. The results of these studies indicate that the [(2-pyridyl)-3-isatin]-bishydrazones possess notable antimicrobial properties.

DOI: 10.1134/S1070363213120360

INTRODUCTION

Hydrazones form an interesting class of chelating compounds which contain an azomethine group linked to a nitrogen atom and which find extensive application in various fields [1, 2], and also form an important class of organic compounds with a wide variety of biological properties [3–7]. Development of new chemotherapeutic hydrazones is now attracting the attention of medicinal chemists [8]. Many studies have been published regarding the biological activity of hydrazones, including their anticancer [9], antibacterial [10], antifungal, and herbicidal action [11, 12].

Isatin (1*H*-indole-2, 3-dione) and its derivatives possess a broad range of biological and pharmacological properties [13–17] and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis [18]. A variety of biological actions are associated with isatin-hydrazones including potentiation of pentobarbitone induced nercosis [19], analgesic [20], anticonvulsant [21], antidepressant [22], anti-inflammatory [23], antimicrobial, and effects on the CNS (central nervous system) [24]. Isatins are capable of crossing the blood–brain-barrier [25].

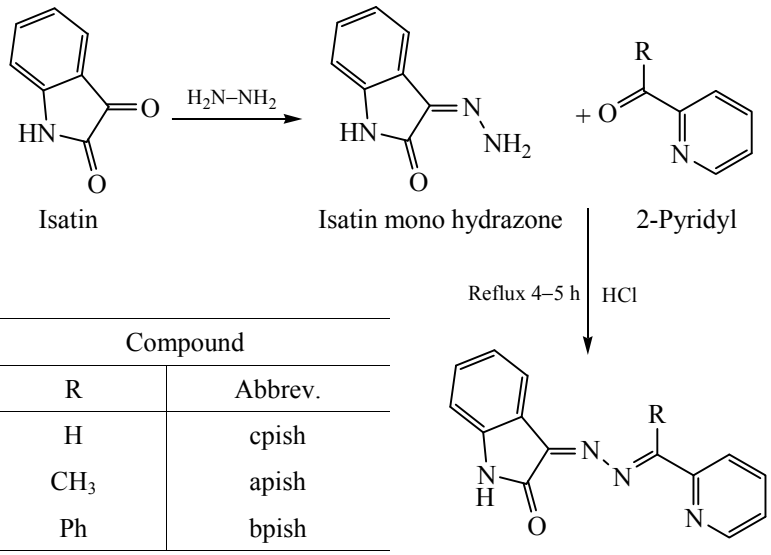
On the other hand, hydrazones of 2-pyridyl derivatives (2-acetylpyridine, 2-benzoylpyridine and pyridine-2-carboxaldhyde) and their metal complexes have good biological applications like antimicrobial [26, 27], anti-inflammatory [28–30], and anticancer [31–33] reagents.

Although much attention has been directed to the study of isatin-hydrazones [34, 35], no publications have appeared describing the hydrazones derived from isatin-monohydrazone and 2-pyridyl derivatives (pyridine-2-carboxaldhyde, 2-acetylpyridine and 2-benzoylpyridine). Therefore the requirement for new isatin-hydrazone derivatives for emerging drug targets is an active area of medicinal chemistry.

Thus, the aim of the present work is to design and characterize new isatin-bishydrazone compounds derived from isatin-monohydrazone and 2-pyridyl derivatives and to assess the antimicrobial and antifungal activity of the synthesized compounds in-vitro against many types of bacterial and fungal cultures, which are common contaminants of the environment in Egypt and some of which are involved in human and animal diseases, plant diseases or frequently reported from contaminated soil, water and food substances.

The structures of the prepared Isatin-bishydrazones compounds in this investigation are shown in Scheme 1.

[1] The text was submitted by the authors in English.



Compound	
R	Abbrev.
H	cpish
CH_3	apish
Ph	bpish

Scheme 1. Schematic diagram of the Isatin-bishydrazones compounds.

EXPERIMENTAL

Chemicals. All chemicals were used as purchased without further purification. Isatin, 2-acetylpyridine, 2-benzoylpyridine and pyridine-2-carboxaldhyde were obtained from Sigma-Aldrich Company Ltd. Hydrazine hydrate was obtained from BDH Company. All other reagents and solvents (methanol, ethanol, and DMF) were purchased from commercial sources and were of analytical grade.

Synthesis of the isatin-bishydrazones compounds. The isatin-bishydrazones, namely [(pyridine-2-carboxaldhyde)-3-isatin]-bishydrazone (cpish), [(2-acetylpyridine)-3-isatin]-bishydrazone (apish), and [(2-benzoylpyridine)-3-isatin]-bishydrazone (bpish) were prepared in two steps: the first step was the synthesis of isatin-monohydrazone, followed by condensation with the 2-pyridyl derivative giving the isatin-bishydrazone ligands.

Synthesis of isatin-monohydrazone. Isatin (1.47 g, 10 mmol) was dissolved in methanol (40 mL) and was added to a solution of hydrazine hydrate (0.05 g, 10 mmol) dissolved in hot methanol (5 mL). The resulting mixture was refluxed for 3 h on a water-bath. On cooling, the yellow compound that formed was filtered off, washed with cold methanol, dried, and recrystallized from methanol [36].

Synthesis of isatin-bishydrazones. 2-Pyridyl derivative (2-acetylpyridine, 2-benzoylpyridine, or pyridine-2-carboxaldhyde) (1.0 mmol) was added dropwise to a hot methanol solution of isatin-monohydrazone (1.0 mmol) the resulting mixture was refluxed for 1h at constant stirring, then 2–3 drops of glacial acetic acid was added and refluxing was continued for 4 h under constant stirring on a magnetic stirrer. On cooling, the precipitated ligand was filtered off, washed with cold methanol, dried, and recrystallized from methanol.

Analyses of the isatin-bishydrazones. The elemental analysis (C, H, and N) of the new compounds was performed using elemental analyzer Perkin-Elmer model 40c at the Micro-analytical Centre at Cairo-University, Egypt. The IR spectra were recorded on Shimadzu FTIR model 8101 spectrophotometer in the region 4000–400 cm^{-1} using dry KBr discs. The electronic spectra in methanol were recorded in the region 200–800 nm using a 10 mm quartz cells on Jasco UV-Visible spectrophotometer model V-530. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solvent (solvent peak ~3.8 ppm) on a Bruker Advance 400 instrument.

In-vitro biological activity. *Antibacterial and anti-fungi screening*. The antimicrobial activity of all synthesized isatin-bishydrazone compounds were tested against 6 bacterial (three gram-positive bacteria and three gram-negative bacteria) and 6 fungal strains. These strains are common contaminants of the environment in Egypt and some of which are involved in human and animal diseases]*Trichophyton rubrum, Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis, Aspergillus flavus* and *Staphylo-*

Table 1. Analytical and physical data of satin-bishydrazones

Compound	Formula (weight)	Color	mp, °C	Yield, %	Elemental analysis		
					C, wt % found (calculated)	H, wt % found (calculated)	N, wt % found (calculated)
cpish	$C_{14}H_{10}N_4O$ (250.255)	red	245°C	89 %	67.19 (67.20)	4.03 (4.33)	22.39 (22.30)
apish	$C_{15}H_{12}N_4O$ (264.28)	red	250°C	85 %	68.17 (68.50)	4.58 (4.25)	21.20 (20.98)
bpish	$C_{20}H_{14}N_4O$ (326.35)	red	265°C	85 %	73.61 (73.55)	4.32 (4.28)	17.17 (17.05)

coccus aureus (+ve)] or in plant diseases (*Fusarium oxysporum*) or frequently reported from contaminated soil, water and food substances [*Escherichia coli* (–ve), *Bacillus cereus* (+ve), *Pseudomonas aeruginosa* (–ve), *Serratia marcescens* (–ve), and *Micrococcus luteus* (+ve)]. To prepare inocula for bioassay, bacterial strains were individually cultured for 48h in 100 mL Erlenmeyer flasks containing 30 mL nutrient broth medium. Fungi were grown for 7 days in 100 mL Erlenmeyer flasks containing 30 mL Sabouraud's dextrose broth. Bioassay was done in 10 cm sterile plastic Petri dishes in which microbial suspension (1 ml/dish) and 15 mL appropriate agar medium (15 mL/dish) were poured. Nutrient agar and Sabouraud's dextrose agar were used for bacteria and fungi respectively. After solidification of the media, 5 mm diameter cavities were cut in the solidified agar (3 cavities/dish) using sterile cork borer. Chemical compounds dissolved in dimethyl sulfuxide (DMSO) at 100 ppm were pipetted in the cavities (20 ul /cavity). Cultures were then incubated at 28°C for 48 h in case of bacteria and up to 7 days in case of fungi. Results were read as the diameter (in mm) of inhibition zone around cavities [37].

Determination of minimum inhibitory concentration (MIC) value. To determine the minimum inhibitory concentrations (MICs), chemical compounds giving positive results were diluted with DMSO to prepare a series of descending concentrations down to 5 ppm. Diluted chemicals were similarly assayed as mentioned before and the least concentration (below which no activity was observed) was recorded as the MIC.

Determination of the activity index (%) for the complexes. The antibacterial and antifungal activity of a common standard antibiotic Chloramphenicol as antibacterial standard and Clotrimazole as antifungal standard were also recorded maintaining the same protocol as above at the same concentrations and solvent. The antibacterial and antifungal results of the compounds were compared with the standard and % activity index for the complexes was calculated by using the below formula [38]:

$$\text{Activity index} = \frac{\text{Zone of inhibition by test compound (diametr)}}{\text{Zone of inhibition by standard (diametr)}} \times 100\%.$$

RESULTS AND DISCUSSION

Identification of the prepared compounds. *Microanalysis measurements*. The results of the microanalysis of the prepared isatin-bishydrazone compounds, suggested that the satisfactory results of analytical data (Table 1) and spectral studies revealed the good purity of ligands and their complexes.

Spectroscopic studies. IR spectra. In the absence of a powerful technique such as single-crystal X-ray diffraction analysis, infrared spectra has proven to be the most suitable technique to give enough information to elucidate the structure and the nature of bonding of the subject isatin-bishydrazones. Thus a detailed interpretation of IR spectra of the isatin-bishydrazones,is presented in Table 2. The IR spectra of the isatin-bishydrazones contained characteristic bands of (-NH) and lactone carbonyl groups ν(C=O) at ~3180–3200 cm^{-1} and ~1722 cm^{-1} [39] respectively. In addition, the strong band at ~1460 cm^{-1} and a characteristic high intensity band at ~ 1621 cm^{-1} in the IR spectrum of the isatin-bishydrazone ligands are assigned to ν(C=N) and ν(HC=N) respectively.

NMR spectra. The NMR spectral data provide valuable information regarding the structure of isatin-bishydrazones. The ^1H NMR and ^{13}C NMR spectra of

Table 2. The infrared absorption frequencies (cm^{-1}) and electronic spectra of the investigated isatin-bishydrazones compounds

Compound	ν(OH)	ν(N–H)	ν(C=O)	ν(HC=N)	ν(C=N)	Electronic spectra[a]		
						λ_{max}, nm	ε_{max}, $dm^3\ mol^{-1}\ cm^{-1}$	Assignment
cpish	3421.2	3276.5	1721.7	1613.7	1460.3	237	1744.05	π–π^*
						324	865.49	n–π^*
apish	3393.2	3180.0	1721.7	1618.5	1458.4	254	538.30	π–π^*
						274	580.97	π–π^*
						325	339.05	n–π^*
bpish	3424.0	3181.0	1721.7	1607.9	1452.6	252	1096.47	π–π^*
						271	882.56	π–π^*
						327	653.87	n–π^*

[a] (λ_{max}) maximum absorbance wavelength, (ε_{max}) molar extinction coefficient.

Table 3. NMR spectral data of the isatin-bishydrazones

Compound	^{1}H NMR chemical shift, δ, ppm (assignment)	^{13}C NMR chemical shift, δ, ppm (assignment)	DEPT ^{13}C NMR chemical shift, δ, ppm
cpish ($C_{14}H_{10}N_4O$)	11.25 s (1H, NH-group) 8.85 s (1H, CH-azomethine) 6.80–8.20 m (8H, aromatic)	164.5 (C=O) 157.4 [β-hydrazone of isatin (C=N)] 153.6 (C=N pyridine ring) 152.3 (–CH=N azomethine) 148.5 (=C–NH) 110–146 (8-CH aromatic)	152.3 110–146
apish ($C_{15}H_{12}N_4O$)	10.70 s, (1H, NH-group) s (1H, CH-azomethine) 6.70–8.50 m (8H, aAromatic) 1.85 s (3H, methyl)	162.3 (C=O) 155. 5 [β-hydrazone of isatin (C=N)] 150.2 (C=N pyridine ring) 149.3 (–C=N azomethine) 147.5 (=C–NH) 110–146 (8-CH aromatic) 18.9 ($–CH_3$ group)	110–146 18.9
bpish ($C_{20}H_{14}N_4O$)	11.15 s (1H, NH-group) s (1H, CH-azomethine) 6.75–8.40 m (13H, aromatic)	165.1 (C=O) 156.3 [β-hydrazone of isatin (C=N)] 155.5 (C=N pyridine ring) 153.7 (–C=N azomethine) 150.5 (13-CH aromatic) 110–149 ($–CH_3$ group)	110–149

the isatin-bishydrazone ligands (in DMSO-d_6) were recorded using tetramethylsilane as the internal reference.

^{1}H NMR and spectra. The ^{1}H NMR spectra of the Isatin-bishydrazones compounds are summarized in Table 3. In ^{1}H NMR spectra the singlet signal at ~10.8–11.0 ppm corresponds to the NH proton of isatin. The azomethine proton appears as a singlet peak at ~ 8.98 ppm in the case of cpish. and disappeared in the other compounds (apish and bpish) due to the substitution of the azomethine proton by methyl or phenyl group in apish and bpish ligands, respectively. Also, all the eight aromatic protons (Isatin ring and pyridine ring) appear as a multiplet in the range ~ 7.80–8.20 ppm. Protons of the methyl group in the case of apish ligand appeared at ~2.37 ppm as a singlet. Also the five aromatic protons of the substituted phenyl ring appeared as multiplet in the range ~ 7.80–8.20 ppm in the case of bpish.

^{13}C NMR spectra. The ^{13}C NMR spectrum of the isatin-bishydrazones and their DEPT–^{13}C NMR are summarized in Table 3. In ^{13}C NMR spectra the

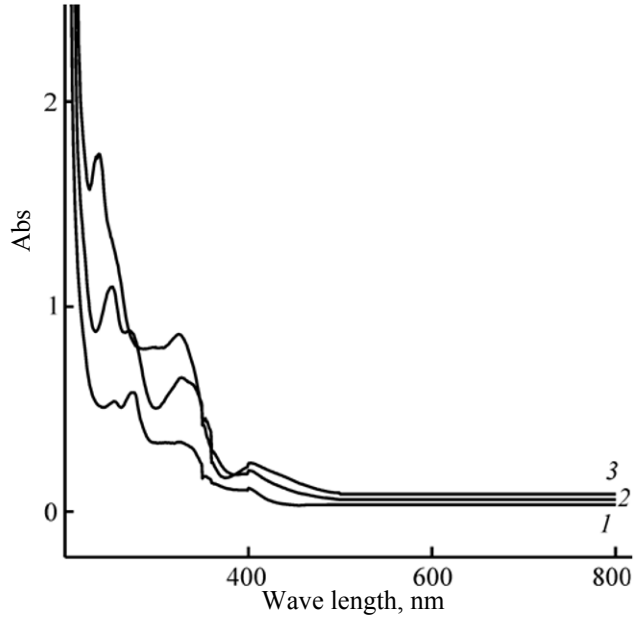


Fig. 1. UV-Vis spectra of the isatin-bishydrazones: (*1*) cpish ligand, (*2*) apish ligand, and (*3*) bpish ligand.

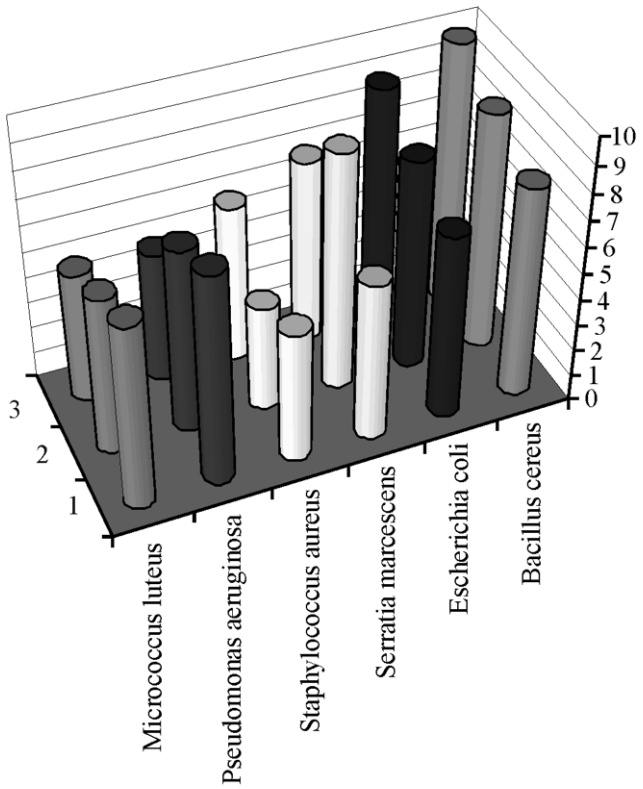


Fig. 2. Antibacterial activity of the synthesized isatin-hydrazone ligands and their Ni(II) complexes.

azomethine carbon appears as a singlet peak at ~149–154 ppm in all compounds, and still as it is in the DEPT–NMR in the case of cpish. and disappeared in the DEPT–NMR of the apish, bpish compounds due to substitution by the methyl and phenyl groups in the apish, bpish, respectively.

Electronic spectra. Electronic spectra are a valuable tool for coordination chemists to draw important information about the structural aspects of the compounds. The isatin-bishydrazones, which are organic compounds, have absorption bands in the ultraviolet region. Electronic spectra of the isatin-bishydrazones were recorded in MeOH (~1×10^{-3} mol/dm^3) in the range 200–800 nm at 298 K. The absorption maxima of the bands are listed in Table 2, and the spectra are given in Fig. 1. The UV-Vis spectra of isatin-bishydrazones show important strong bands at ~ 388 and ~230 nm due to π–π^* and n–π^* transitions [40] respectively.

Table 4. Antibacterial activity of the isatin-bishydrazones compounds

Comp. no.	Conc., ppm	Diameter of inhibition zone (mm), minimum inhibition concentration (MIC), and activity index (%) for some bacteria																	
		Gram-positive bacteria									Gram-negative bacteria								
		Staphylococcus aureus (+ve)			*Micrococcus Luteus* (+ve)			*Bacillus cereus* (+ve)			*Escherichia coli* (–ve)			*Pseudomonas aeruginosa* (–ve)			*Serratia marcescens* (–ve)		
		mm	MIC	%	mm	MIC	%	mm	MIC	%	Mm	MIC	%	mm	MIC	%	mm	MIC	%
cpish	100	6	45	40	5	50	35.7	10	40	45.4	9	50	45	5	45	25	7	50	38.8
apish	100	4	40	26.7	6	45	42.8	9	55	40.9	8	45	40	7	50	35	9	55	50
bpish	100	5	50	33.3	7	40	50	8	45	36.4	7	45	35	8	50	40	6	50	33.3
Chloramphenicol (as antibacterial standard)		15		100	14		100	22		100	20		100	20		100	18		100

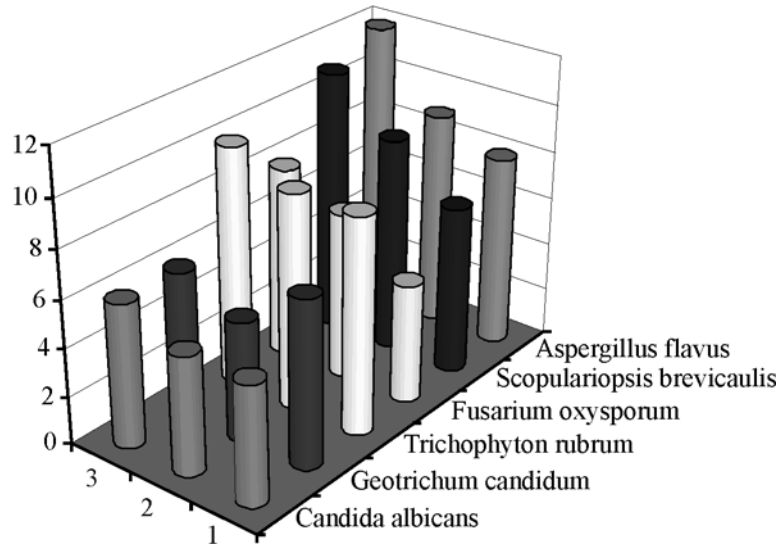


Fig. 3. Antifungal activity of the synthesized isatin-hydrazone ligands and their Ni(II) complexes.

3.2. In-vitro biological activity (antibacterial and anti-fungi screening). The isatin-bishydrazones compounds were screened for antibacterial activity against three gram positive [*Staphylococcus aureus* (+ve), *Micrococcus luteus* (+ve), *Bacillus cereus* (+ve)], and three gram negative [*Escherichia coli* (–ve), *Pseudomonas aeruginosa* (–ve), Serratia marcescens (–ve)] and also for antifungal activity against *Candida albicans, Geotrichum candidum, Trichophyton rubrum, Fusarium oxysporum, Scopulariopsis brevicaulis, Aspergillus flavus* to assess their potential activity. The susceptibilities of certain strains of bacteria and fungal cultures to isatin-bishydrazones compounds were evaluated by measuring the diameter (in mm) of the inhibition zone around cavities. The antimicrobial activity data of all synthesized isatin-bishydrazones compounds are summarized in Tables 4 and 5, Figs. 2, 3 and show that the newly synthesized isatin-bishydrazones compounds possess notable biological activity. This activity can be rationalized on the basis of the structures of the isatin-bishydrazones possessing an additional azomethine (–C=N) linkage which is important in elucidating the mechanism of transamination and resamination reaction in biological systems [41]. It has also been suggested that the isatin-bishydrazones with nitrogen and oxygen atoms in the system might inhibit enzyme production [42]. The results are quite promising. Isatin-bishydrazones have good biological activity and act as powerful and potent bactereostatic agents, thus inhibiting the growth of bacteria and fungi.

Table 5. Antifungal activity of the isatin-bishydrazones

Comp. no.	Conc., ppm	Diameter of inhibition zone (mm), minimum inhibition concentration (MIC), and activity index (%) for some bacteria																	
		Gram-positive bacteria									Gram-negative bacteria								
		Candida albicans			*Geotrichum candidum*			*Trichophyton rubrum*			*Fusarium oxysporum*			*Scopulariopsis brevicaulis*			*Aspergillus flavus*		
		mm	MIC	%	mm	MIC	%	mm	MIC	%	Mm	MIC	%	mm	MIC	%	mm	MIC	%
cpish	100	6	40	42.8	6	55	30	10	40	33.3	8	30	44.4	11	40	45.8	12	45	40
apish	100	5	50	35.7	5	45	25	9	30	30	7	35	38.9	9	50	37.5	9	55	30
bpish	100	5	55	35.7	7	50	35	9	35	30	5	40	27.8	7	45	29.2	8	40	26. 7
Clotrimazole (as antifungal standard)		14		100	20		100	30		100	18		100	24		100	30		100

REFERENCES

1. Mariar, C.R., Belicchi, F.M., Franco, B., Corrado, P., Giorgio, P., Silvana, P., and Monica, S., *J. Inorg. Biochem.,* 2004, vol. 98, pp. 313–321.
2. Sridhar, S.K. and Ramesh, A., *Biol. Pharm. Bull*., 2001, vol. 24, pp. 1149–1152.
3. Lozier, R.; Bogomolni, R.A.; and Stoekenius, W., *J. Biophys*., 1975, no. 15, p. 955.
4. Garnovskii, A.D.; Nivorozhkin, A.L.; and Minkin, V.I., *Coord. Chem. Rev*., 1993, no. 1 , p. 126.
5. Costamagna, J.; Vargas, J.; Latorre, R.; Alvarado, A.; and Mena, G., *Coord. Chem. Rev*., 1992, vol. 67, p. 119.
6. Walsh, C.T. and Orme-Johnson, W.H., *Biochemistry*, 1987, vol. 26, p. 4901
7. (a) Witkop, B. and Ramachandran, L.K., *Metabolism*, 1964, no. 13, p. 1016; (b) Morton, R.A. and Pitt, G.A.J., *J. Biochem.,* 1955, vol. 59, p. 128; (c) Grazi, E., Rowley, R.T., Cheng, T., Tchola, O., and Horecker, B.L., *Biochem. Biophys. Res. Commun*., 1962, no. 9, p. 38; (d) Fridovitch, I. and Westheimer, F.H., *J. Am. Chem. Soc*., 1962, vol. 84, p. 3208; (e) Hammes, G.G. and Fasella, P., *J. Am. Chem. Soc*., 1962, vol. 84, p. 4644; (f) Tovrog, B.S., Kitko, D.J., and Drago, R.S., *J. Am. Chem. Soc*., 1976, vol. 98, p. 5144
8. Katia, B., Simon, L., Anne, R., Gerard, C., Francoise, D., and Bernard, M., *Inorg. Chem*., 1996, vol. 35, p. 387.
9. Solomon, E.I. and Lowery, M.D., *Science*, 1993, vol. 259, p. 1575.
10. Gerdemann, C., Eicken, C., and Krebs, B., *Chem. Res*., 2002, vol. 35, p. 183.
11. Mallikarjun, S.Y. and Sangamesh, A.P., *Transition Met. Chem*., 1997, vol. 22, p. 220.
12. Yang, G.W., Xia, X.P., Tu, H., and Zhao, X.C., *Chem. Res. Appl*., 1995, no. 7, p. 41
13. Daisley, R.W. and Shah, V.K., *J. Pharm. Sci*., 1984, vol. 73, p. 407.
14. Pandeya, S.N., Sriram, D., Declecq, E., Pannecouque, C., and Mitvrouw, M., *Indian J. Pharm. Sci*., 1999, vol. 60, p. 207.
15. Pandeya, S.N. and Dimmock, J.R., *Pharmazie*, 1993, vol. 48, p. 659.
16. Boon, R., *Antiviral Chem. Chemother*., 1997, no. 8, p. 5.
17. Pandeya, S.N., Siram, D., Nath, G., and Declercq, E., *Eur. J. Pharm. Sci*., 1999, no. 9, p. 25.
18. Khan, K.M., Khan, M., Ali, M., Taha, M., Rasheed, S., Perveen, S., and Choudhary, M.I., *Bioorg. Med. Chem*., 2009, no. 17, pp. 7795–7801
19. Sarangapani, M., Reddy, N.A., Jayamma, Y., and Reddy, V.M., *Indian Drugs*, 1998, vol. 35, p. 336.
20. (a) Sarangapani, M. and Reddy, V.M., *Indian Drugs*, 1999, vol. 36, p. 357; (b) Sarangapani, M. and Reddy, V.M., *Indian J. Pharm. Sci*., 1996, vol. 58, p. 147.
21. (a) Sarangapani, M. and Reddy, V.M., *Indian J. Pharm. Sci*., 1997, vol. 59, p. 105; (b) Popp, F.D., Parson, R., and Donigan, B.E., *J. Heterocycl. Chem.*, 1980, no. 17, p. 1329; (c) Popp, F.D., Parson, R., and Donigan, B.E., *J. Pharm. Sci*., 1980, vol. 69, p. 1235; (d) Pajouhesh, H., Parson, R., and Popp, F.D., *J. Pharm. Sci*., 1983, vol. 72, p. 318; (e) Popp, F.D. and Pajouhesh, H., *J. Pharm. Sci*., 1982, vol. 71, p. 1052; (f) Bhattacharya, S.K., *Indian J. Exp. Biol*., 1998, vol. 36, p. 118.
22. Singh, G.S., Singh, T., and Lakhan, R., *Indian J. Chem., Sect. B*, 1997, vol. 36, p. 951
23. (a) Lingaiah, N., Narendra, R., and Dattatray, A.M., *Indian J. Chem., Sect. B*, 1998, vol. 37, p. 1254; (b) Andreani, A.M., *Bull. Chim. Farm*., 1977, vol. 116, p. 493.
24. (a) Medvedec, A.E., Clow, A., Sandler, M., and Glover, V., *Biochem. Pharmacol.*, 1998, vol. 52, p. 385; (b) Glover, V., Halket, J.M., Watkins, P.J., Clone, A., Goodwin, B., and Sandler, A., *J. Neurochem.*, 1998, vol. 51, p. 656.
25. Panova, N.G., Zemskova, M.A., Axenova, L.N., and Medevedev, A.E., *Neurosci. Lett*., 1997, vol. 223, p. 58.
26. Vicini, P., Zani, F., Cozzini, P., and Doytchinova, I., *Eur. J. Med. Chem*., 2002, vol. 37, pp. 553–564.
27. Despaigne, A.A.R., Vieira, L.F., Mendes, I.C., Da Costa, F.B., Speziali, N.L., and Beraldo, H., *J. Braz. Chem. Soc*., 2010, vol. 21, pp. 1247–1257.
28. Moldovan, C.M., Oniga, O., Pârvu, A., Tiperciuc, B., Verite, P., Pîrnau, A., Cris¸ O., Boji, M., and Pop, R., *Eur. J. Med. Chem*., 2011, vol. 46, pp. 526–534.
29. Eissa, A.A.M., Farag, N.A.H. , and Soliman, G.A.H., *Bioorg. Med. Chem*., 2009, vol. 17, p. 5059-50
30. Hoonur, R.S., Patil, B.R., Badiger, D.S., Vadavi, R.S., Gudasi, K.B., Dandawate, P.R., Ghaisas, M.M., Padhye, S.B., and Nethaji, M., *Eur. J. Med. Chem.*, 2010, vol. 45, pp. 2277–2282.
31. Lovejoy, D.B. and Richardson, D.R., *Blood*, 2002, vol. 100, pp. 666–676.
32. Richardson, D.R., Tran, E.H., and Ponka, P., *Blood*, 1995, vol. 86, pp. 4295–4306.
33. Savini, L., Chiasserini, L., Travagli, V., Pellerano, C., Novellino, E., Cosentino, S., and Pisano, M.B., *Eur. J. Med. Chem*., 2004, vol. 39, pp. 113–122.
34. Garg, B.S., Singh, P.K., and Garg, S.K., *Indian J. Chem. A*, 1991, vol. 30, p. 979.
35. Abu El-Reash, G.M., Taha, F., Shallaby, A.M., and El-Gamal, O.A., *Indian J. Chem. A*, 1991, vol. 30, p. 286.
36. Kulkarni, A.D., Patil, S.A., and Badami, P.S., *Int. J. Electrochem. Sci*., 2009, no. 4, pp. 717–729.
37. *Kwon- Chung and Bennett*, 1992.
38. Singh, V.P. and Katiyar, A., *Pesticide Biochemistry and Physiology*, 2008, vol. 92, pp. 8–14.
39. Neena, S., Sunita, H., Jyoti, S., Vanita, P., and Agarwala, B.V., *Synth. React. Inorg. Met.-Org. Chem.,* 1992, vol. 22, p. 1283.
40. Nakamoto, K., *Infrared Spectra of Inorganic and Coordination Compounds*, New York: Wiley-Interscience, 1970.
41. Nishat, N., Hasnain, S., and Asma, S.D., *J. Coord. Chem.,* 2010, vol. 63(21), pp. 3859–3870.
42. Chohan, Z.H., Supuran, C.T., and Scozzafava, A., *J. Enz. Inhib. Med. Chem*., 2004, vol. 9, pp. 79–84.