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Research Article

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Synthesis, characterization, antimicrobial studies of certain piperazine containing s-triazine derived compound

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ABSTRACT

Some new substituted 1,3,5 triazine with Chloro benzhydryl piperazine and substituted urea/thiourea were synthesized and evaluated for their in vitro antimicrobial activity against Gram positive and Gram negative strains using a microdilution procedure. Synthesized compounds 2a to 2k prove to be effective with MIC (μg/ml), among them 2b, 2d, 2g showed good activity against a panel of microorganisms. The newly synthesized compounds were characterized using IR, ^{1}H-NMR.

Keywords: Chloro benzhydryl piperazine, Substituted urea/thiourea, Cyanuric chloride and Antimicrobial activity

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INTRODUCTION

In this work, we report the synthesis and biological activity of some newly synthesized cyanuric chloride based derivatives.

s-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals[1], anticancer agents[2], estrogen receptor modulators[3], antimalarials[4], cyclin-dependent kinase modulators[5], and antimicrobials[6]. Cyanuric chloride derivatives are widely used in commercial chemicals, Some trisubstituted-1,3,5-triazines are also used as liposome[7]. Several investigators found s-triazine nucleus as potential therapeutic agents for diseases due to bacteria, malaria and cancer[8]. 1,3,5-Triazine derivatives have displayed a broad range of biological activities antiangiogenic activity by targeting either VEGF-R2 (KDR)[9] or direct modulation of Tie-2 tyrosine kinase phosphorylation[10], antiparasitic activities[11,12], and glucocerebrosidase inhibition with potential as chemical chaperones for Gaucher disease[13].

Thiourea derivatives possess antibacterial[14], hypnotic antitubercular and possible anticonvulsant activities. It also represent a new class of human immuno deficiency virus type (HIV-1), non-nucleoside reverse transcriptase (NNRT)

inhibitors[15], found as antagonist[16], and high density lipoprotein (HDL) elevating agents[17].

Piperazine is a main moiety in psychoactive drugs. Certain piperazine derivatives are suspected of ecstasy substitutes. Benzylpiperazine is banned in many countries. Benzylpiperazine has been used as a anthelmintic (antiparastic effect). Nitrogen in piperazine ring plays an important role in biological research and drug manufacturing industry.

We planned to undertake the synthesis and characterization of some triazine derivatives carrying the above biodynamic heterocyclic systems with the hope to achieve enhanced biological activity.

EXPERIMENTAL SECTION

General

All the melting points were taken in open capillaries tube and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) Using silica gel – G coated Al – plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra were recorded on FTIR spectrophotometer using KBr or Nujol technique. ^{1}H NMR spectra on a Varian 400 FT MHz NMR instrument at using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference.

SCHEME

STEP-1

PREPARATION OF 1-(2-CHLOROPHENYL)-3-(4,6-DICHLORO-1,3,5-TRIAZIN-2-YL)UREA : (A)

To a stirred solution of cyanuric chloride (0.1 mole, 18.4 g) in DMF (100 ml) at 0-5^{0}C, the solution of 2- chloro phenyl urea(0.1 mole, 15.78 g) in DMF (25 ml) was added and pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. The stirring was continued at 0-5°C for 2 hours. After the completion of reaction the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get title compound.

STEP-2

PREPARATION OF 1-(4_CHLORO-6-(4((4-CHLOROPHENYL) (PHENYL)METHYL) PIPERAZINE-1-YL)-1,3,5-TRIAZIN-2-YL)-3-(2-CHLOROPHENYL) UREA :(B)

To a stirred solution of (A) (0.1 mole, 31.8 g) in DMF (100 ml) was added, the solution of Chloro benzhydryl piperazine (0.1 mole, 28.6g) in DMF (30 ml) was added drop wise maintaining the temperature at 40°C, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. The temperature was gradually raised to 45°C during two hours. After the completion of reaction, the resultant content was poured into ice-cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get the title compound.

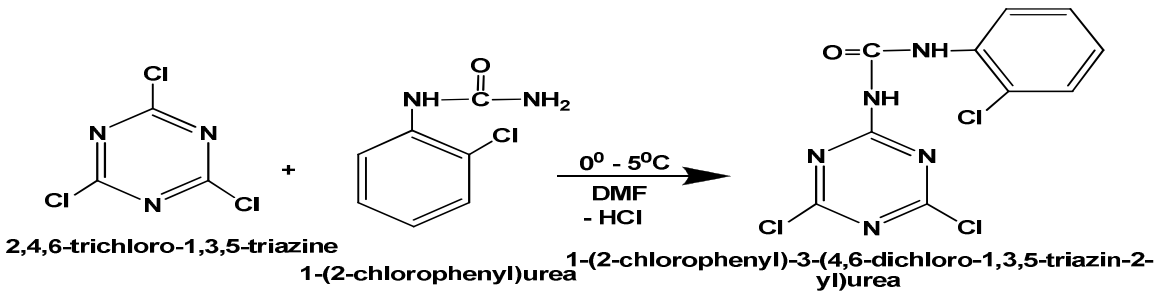
STEP-3

PREPARATION OF FINAL COMPOUNDS :(C)

A mixture of (B) (0.01 mole, 5.67g) and aryl thiourea (0.01 mole) in DMF (10ml) was refluxed in oil bath. The temperature was gradually raised to 80-100^{0}C during four hours, the pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per requirement of reaction condition. After the completion of reaction, add little charcoal in R.B.F. and heat the refluxed content and then filter to cold water. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol.

ROUTE OF SYNTHESIS

STEP-1



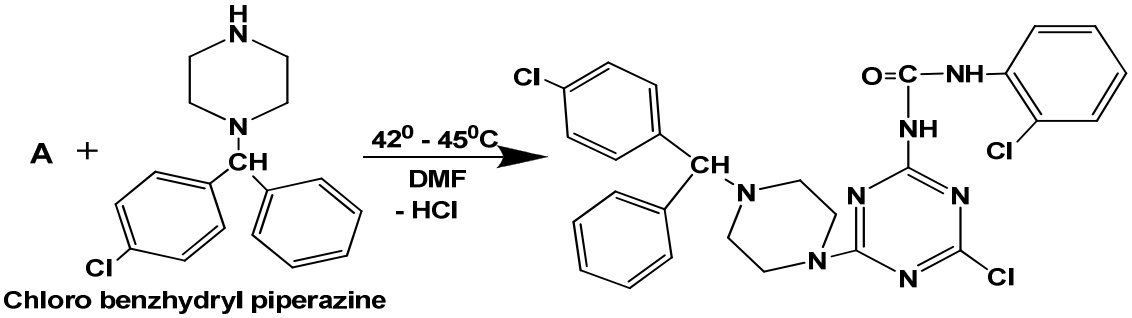
2,4,6-trichloro-1,3,5-triazine

1-(2-chlorophenyl)urea

1-(2-chlorophenyl)-3-(4,6-dichloro-1,3,5-triazin-2-yl)urea

[A]

STEP-2

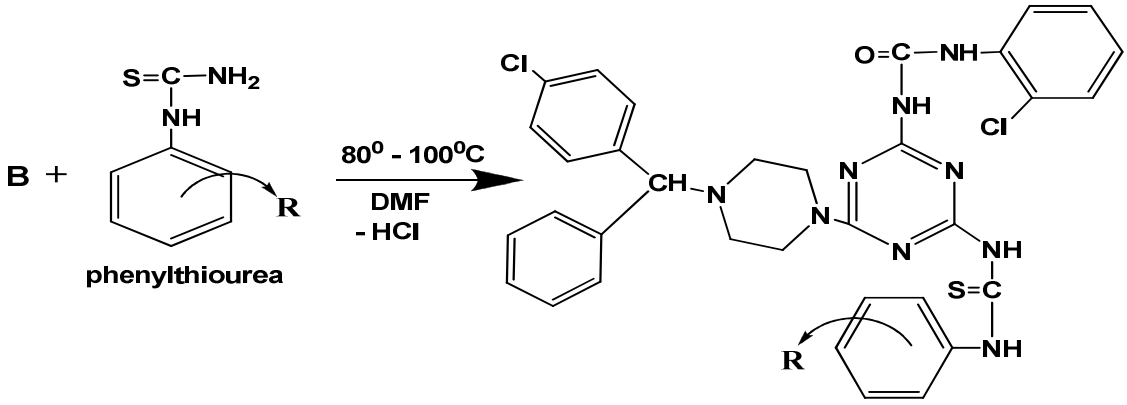


Chloro benzhydryl piperazine

1-(4-chloro-6-(4-((4-chlorophenyl)(phenyl)methyl) piperazin-1-yl)-1,3,5-triazin-2-yl)-3-(2-chlorophenyl)urea

[B]

STEP-3



phenylthiourea

1-(2-chlorophenyl)-3-(4-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-6-(3-phenylthioureido)-1,3,5-triazin-2-yl)urea

Where **R** = given in below table.

Table 1 Physical Data Of Synthesized Compounds

Sr. No.		R	Mol. Formula	Mol. Weight	M.P. ^{O}C	Yield %
1.	2a	H	$C_{34}H_{31}Cl_2N_9OS$	684.64	130	56.1
2.	2b	2-OCH_3	$C_{35}H_{33}Cl_2N_9O_2S$	714.67	120	58.8
3.	2c	4-OCH_3	$C_{35}H_{33}Cl_2N_9O_2S$	714.67	125	60.4
4.	2d	2-CH_3	$C_{35}H_{33}Cl_2N_9OS$	698.67	190	50.2
5.	2e	4-CH_3	$C_{35}H_{33}Cl_2N_9OS$	698.67	118	57.2
6.	2f	2-Cl	$C_{34}H_{30}Cl_3N_9OS$	719.09	100	58.1
7.	2g	3-Cl	$C_{34}H_{30}Cl_3N_9OS$	719.09	115	62.2
8.	2h	4-Cl	$C_{34}H_{30}Cl_3N_9OS$	719.09	120	61.1
9.	2i	4-NO_2	$C_{34}H_{30}Cl_2N_{10}O_3S$	729.64	150	59.0
10.	2j	α-phenyl	$C_{38}H_{33}Cl_2N_9OS$	734.70	125	65.5
11.	2k	3,5 Di Cl	$C_{34}H_{29}Cl_4N_9OS$	753.53	145	70.0

Compound (2a):

Yield:56.1%; m.p. 130^{0}C (dec.); **IR(KBr,cm^{-1}) :** 697.79 cm^{-1}(mono sub benzene)712 cm^{-1}(-C-Cl- str in Ar ring)800 cm^{-1}(-C=N- str in s-triazine)985 cm^{-1}(1:4- Di sub benzene)1369.16 cm^{-1}(Ar 3^{0}amine)1514.08 cm^{-1}(-C=S- str in thiourea)1570.90 cm^{-1}(-NH- def in 2^{0}amine)1601.16 cm^{-1}(>C=O str in urea)2915.30 cm^{-1}(C-H str as CH)3444.79 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.24(s,1H, -CH),3.61(s,4H, -CH_2),7.26 to 7.43(m,18H, Ar-H),8.41(s,2H, -NH),10.14(s,2H,-NH).

Compound (2b):

Yield: 58.8%; m.p. 120^{0}C (dec.); **IR (KBr,cm^{-1}) :** 698.15 cm^{-1}(mono sub benzene)714.5 cm^{-1}(-C-Cl- str in Ar ring)801 cm^{-1}(-C=N- str in s-triazine)987.12 cm^{-1}(1:4- Di sub benzene)1364.61 cm^{-1}(Ar 3^{0}amine)1510.28 cm^{-1}(-C=S- str in thiourea)1574.21 cm^{-1}(-NH- def in 2^{0}amine)1604.36 cm^{-1}(>C=O str in urea)2917.90 cm^{-1}(C-H str as CH)3440.10 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.30(s,1H, -CH),3.61(s,4H, -CH_2),7.04 to 7.23(m,17H, Ar-H), 8.42(s,2H, -NH), 10.15(s,2H,-NH),4.37(s,3H,-OCH_3).

Compound (2c):
Yield: 60.4%; m.p. 125^{0}C (dec.); **IR (KBr,cm^{-1}) :** 699.29 cm^{-1}(mono sub benzene)717.86 cm^{-1}(-C-Cl- str in Ar ring)802.45 cm^{-1}(-C=N- str in s-triazine)980.86 cm^{-1} (1:4- Di sub benzene)1367.16 cm^{-1}(Ar 3^{0}amine)1515.78 cm^{-1}(-C=S- str in thiourea)1572.93 cm^{-1}(-NH- def in 2^{0}amine)1601.16 cm^{-1}(>C=O str in urea)2849.19 cm^{-1}(C-H str as –OCH_3) 2915.30 cm^{-1}(C-H str as CH)3444.79 cm^{-1}(-NH- str 2^{0}amine) **^{1}H-NMR:δ** 2.32(s,1H,-CH), 3.70(s,4H,-CH_2),7.30to7.59(m,17H,Ar-H),8.41(s,2H,-NH),10.17(s,2H,-NH),4.35(s,3H,-OCH_3).

Compound (2d):
Yield: 50.2%; m.p. 190^{0}C (dec.); **IR (KBr,cm^{-1}) :** 698 cm^{-1}(mono sub benzene) 714.5cm^{-1}(-C-Cl- str in Ar ring) 802.09 cm^{-1}(-C=N- str in s-triazine) 988.21 cm^{-1}(1:4- Di sub benzene) 1324 cm^{-1} (-C-CH_3 str)1368.98 cm^{-1}(Ar 3^{0}amine) 1512.78 cm^{-1}(-C=S- str in thiourea) 1571 cm^{-1}(-NH- def in 2^{0}amine) 1600 cm^{-1}(>C=O str in urea)2917 cm^{-1}(C-H str as CH)3439cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.35(s,1H,-CH),3.69(s,4H, -CH_2),3.74(s,3H,at -CH_3),7.41 to 7.63(m,17H,Ar-H),8.40(s,2H,-NH),10.20(s,2H,-NH), 4.37(s,3H,-CH).

Compound (2e):
Yield: 57.2%; m.p. 118^{0}C (dec.); **IR (KBr,cm^{-1}) :** 700.01 cm^{-1}(mono sub benzene) 710.01 cm^{-1}(-C-Cl- str in Ar ring) 804.32 cm^{-1}(-C=N- str in s-triazine) 980.05 cm^{-1} (1:4- Di sub benzene) 1320 cm^{-1} (-C-CH_3 str)1375 cm^{-1}(Ar 3^{0}amine) 1519 cm^{-1}(-C=S- str in thiourea) 1574.40 cm^{-1}(-NH- def in 2^{0}amine) 1600.35 cm^{-1}(>C=O str in urea)2921.90 cm^{-1}(C-H str as CH)3449 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.22(s,1H, -CH), 3.62(s,4H, -CH_2), 3.71(s,3H,at –CH_3),7.42 to 7.73(m,17H, Ar-H),8.55(s,2H,-NH),10.17(s,2H,-NH),4.40 (s,3H,-CH).

Compound (2f):
Yield: 58.1%; m.p. 100^{0}C (dec.); **IR (KBr,cm^{-1}) :** 691 cm^{-1}(mono sub benzene) 710 cm^{-1}(-C-Cl- str in Ar ring) 808 cm^{-1}(-C=N- str in s-triazine) 990.07 cm^{-1}(1:4- Di sub benzene) 1376.12 cm^{-1}(Ar 3^{0}amine) 1514.08 cm^{-1}(-C=S- str in thiourea) 1567.12 cm^{-1} (-NH- def in 2^{0}amine) 1604 cm^{-1}(>C=O str in urea)2920 cm^{-1}(C-H str as CH) 3437 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.35(s,1H, -CH), 3.60(s,4H, -CH_2),7.21to 7.53(m,17H, Ar-H), 8.48(s,2H, -NH), 10.24(s,2H,-NH), 4.31(s,3H,-CH).

Compound (2g):
Yield: 62.2%; m.p. 115^{0}C (dec.); **IR (KBr,cm^{-1}) :** 702.14 cm^{-1}(mono sub benzene) 716 cm^{-1}(-C-Cl- str in Ar ring) 810 cm^{-1}(-C=N- str in s-triazine) 992 cm^{-1}(1:4- Di sub benzene) 1380.01 cm^{-1}(Ar 3^{0}amine) 1525 cm^{-1}(-C=S- str in thiourea) 1578.37 cm^{-1}(-NH- def in 2^{0}amine) 1609.09 cm^{-1}(>C=O str in urea)2923.31 cm^{-1}(C-H str as CH) 3455 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.30(s,1H, -CH),3.61(s,4H, -CH_2),7.20 to 7.40(m,17H, Ar-H),8.43(s,2H, -NH),10.14(s,2H,-NH), 4.39 (s,3H,-CH).

Compound (2h):
Yield: 61.1%; m.p. 120^{0}C (dec.); **IR (KBr,cm^{-1}) :** 688.79 cm^{-1}(mono sub benzene) 719.32 cm^{-1}(-C-Cl- str in Ar ring) 814.12 cm^{-1}(-C=N- str in s-triazine) 991 cm^{-1} (1:4- Di sub benzene)1380.05 cm^{-1}(Ar 3^{0}amine) 1519.09 cm^{-1}(-C=S- str in thiourea) 1579.70 cm^{-1}(-NH- def in 2^{0}amine) 1609.90 cm^{-1}(>C=O str in urea)2920.06 cm^{-1}(C-H str as CH) 3455.09 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.34(s,1H, -CH),3.62 (s, 4H,-CH_2),7.30 to 7.63(m,17H, Ar-H), 8.57(s,2H, -NH), 10.14 (s,2H,-NH),4.41(s,3H,-CH).

Compound (2i):
Yield: 59%; m.p. 150^{0}C (dec.); **IR (KBr,cm^{-1}) :** 706.69 cm^{-1}(mono sub benzene) 718 cm^{-1}(-C-Cl- str in Ar ring) 798.92 cm^{-1}(-C=N- str in s-triazine) 975 cm^{-1}(1:4- Di sub benzene) 1368 cm^{-1}(Ar 3^{0}amine) 1510.78 cm^{-1}(-C=S- str in thiourea) 1563.80 cm^{-1}(-NH- def in 2^{0}amine) 1598.96 cm^{-1}(>C=O str in urea)2930.70 cm^{-1}(C-H str as CH) 3457.12 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.29(s,1H,-CH),3.58(s,4H,-CH_2),7.31 to 7.63(m,17H, Ar-H),8.56(s,2H, -NH),10.18(s,2H,-NH),4.42(s,3H,-CH).

Compound (2j):
Yield: 65.5%; m.p. 125^{0}C (dec.); **IR (KBr,cm^{-1}) :** 708.65 cm^{-1}(mono sub benzene) 704.24 cm^{-1}(-C-Cl- str in Ar ring) 810.05 cm^{-1}(-C=N- str in s-triazine) 994.41 cm^{-1} (1:4- Di sub benzene)1374.42 cm^{-1}(Ar 3^{0}amine) 1515.58 cm^{-1}(-C=S- str in thiourea) 1585.90 cm^{-1}(-NH- def in 2^{0}amine) 1612.16 cm^{-1}(>C=O str in urea)2925.50 cm^{-1}(C-H str as CH) 3434.19 cm^{-1}(-NH- str in 2^{0}amine) **^{1}H-NMR:δ** 2.36(s,1H, -CH),3.60(s,4H, -CH_2), 7.26 to 7.52(m,20H, Ar-H),8.54(s,2H, -NH), 10.16 (s,2H,-NH),4.45(s,3H,-CH).

Compound (2k):
Yield: 70%; m.p. 145^{0}C (dec.); **IR (KBr,cm^{-1}) :** 699.99 cm^{-1}(mono sub benzene) 707.35 cm^{-1} (-C-Cl- str in Ar ring) 814.12 cm^{-1}(-C=N- str in s-triazine) 995.12 cm^{-1} (1:4- Di sub benzene) 1387.36 cm^{-1}(Ar 3^{0}amine)1519.08 cm^{-1}(-C=S- str in thiourea) 1580.90 cm^{-1}(-NH- def in 2^{0}amine) 1615.56 cm^{-1}(>C=O str in urea)2930.40 cm^{-1}(C-H str as

CH) 3456.41 cm^{-1}(-NH- str in 2^0amine) **^{1}H-NMR:δ** 2.34(s,1H, -CH), 3.61 (s,4H,-CH_2),7.40 to 7.93(m,16H, Ar-H),8.54(s,2H, -NH), 10.20 (s,2H,-NH),4.45(s,3H,-CH).

RESULTS AND DISCUSSION

ANTIMICROBIAL ACTIVITY

For the testing antimicrobial activity various microorganism were used for the study. The **broth dilution** method was used for this study. Following general procedure is adopted. The antimicrobial activity of all the compounds was studies at 1000 ppm concentration *in vitro*. The test compound is first dissolved in suitable media or solvent. DMSO has been used in all the cases for present work to keep uniformity. Also, most of the compounds synthesized are water insoluble. 10 mg of the test compound is dissolved in DMSO so as to make necessary dilutions as 1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.8 µg/ml from the stock solutions of the compounds to be tested. The different types of microorganism used were some gram negative bacteria [*Escherichia coli, Pseudomonas aeruginosa*], gram positive bacteria [*Bacillus subtilis*, *Staphylococcus aureus*] and fungus [*Candida albicans*].

80% DMSO are used as solvent to dissolve compound 2a to 2k to 10**(µg/ml).**

Minimum Inhibitory Concentration (µg/ml)							
Sr. No	Comp. No	R	Gram positive bacteria		Gram negative bacteria		Fungus
			S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C.albicans*
1.	2a	H	125	125	125	125	62.5
2.	2b	2-OCH_3	62.5	125	250	125	125
3.	2c	4-OCH_3	125	125	125	125	125
4.	2d	2-CH_3	62.5	125	125	125	125
5.	2e	4-CH_3	125	125	250	125	62.5
6.	2f	2-Cl	125	125	125	250	125
7.	2g	3-Cl	62.5	125	250	250	125
8.	2h	4-Cl	62.5	125	125	250	125
9.	2i	4-NO_2	62.5	125	125	125	125
10.	2j	α-phenyl	125	125	250	125	250
11.	2k	3,5 di Cl	62.5	125	250	125	125
12.	Ciprofloxacin		7.8	7.8	7.8	7.8	------
14.	Flucanazole		-----	-----	-----	-----	15.62

CONCLUSION

A series of cyanuric chloride derivatives were prepared and tested for their *in vitro* antibacterial activity against the four strains of bacteria (gram +ve, gram –ve).Three compounds of the obtained series showed high *in vitro* antimicrobial activity. Maximum compounds showed excellent activity against *Staphylococcus aureus.* Whereas compound 2a and 2e have excellent activity against *C. albicans.*

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REFERENCES

[1] A. Balini; G.J. Bueno; M.L. Stewart;V. Yardley; R. Brun; P.M. Barrett. *J. Med. Chem.* **2005**, 48, 5570–5579.
[2] R. Menicagli; S. Samaritani; G. Signore; F. Vaglini. *J. Med. Chem*. **2004**, 47, 4649–4652.
[3] B.R. Henke; T.G. Consler; N.Go; R.L Hale. *J. Med. Chem.* **2002**, 45, 5492–5505.
[4] A. Agarwal; K.Srivastava; S.K. Puri; P.M.S Chauhan. *Bio org. Med. Chem. Lett.* **2005**, 15, 531–533.
[5] G.H. Kuo; A.DeAngelis; S. Emanuel; A. Wang; Y. Zhang. *J. Med. Chem*. **2005**, 48, 4535–4546.
[6] Z.E. Koc; H. Bingol; A.O. Saf; E. Torlak; A. Coskum. *J. Hazard. Mater*. **2010,** 183, 251–255.
[7] K. Barkhard and I.H. Gilbert**.** *J. Med. Chem.*, **2001**, 44, 3440.
[8] G.Candiani; M. Frigerio; F.Viani; C. Verpelli; C. Salay; L.Chiamenti; N. Zaffaroni; M. FolinI.*Chem. Med. Chem*.**2007,** 2, 292-296.
[9] N.Baindur; N. Chadha; B.M. Brandt; D. AsgarI; R.J.Patch. *J. Med. Chem*. **2005**, 48, 1717–1720.
[10] B.L. Hodous; S.D. Geuns-Meyer; P.E. Hughes. *J. Med. Chem.* **2007**, 50, 611–626.
[11] A. Agarwal; K. Srivastava; S.K. Puri; P.M.S. Chauhan. *Bio org., Med Chem. Lett* **2005**, 15, 531–533.
[12] A. Baliani; G.J. Bueno; M.L. Stewart; V. Yardley; R. Brun; M.P. Barrett; I.H. Gilbert.*J. Med. Chem*. **2005**, 48, 5570–5579.
[13] W.Huang; W. Zheng; D.J. Urban; J. Inglese. *Bio org. Med. Chem. Lett*. **2007**, 17, 5783–5789.
[14] K.H. Chikhalia and K.R.Desai. *Acta. Cienecia. Indica.*, **1998**, XXIV C.

[15] G.Campiani; M. Fabbrini and S. Caccia. *J. Med. Chem.* **2001**, 44, 305.
[16] J. Lee and P.M. Blamberg. *J. Med. Chem*. **2001**, 46, 3116.
[17] C.M. Cappola; R.E. Damon. *Bio org. and Med. Chem. Lett*., **2005**, 15, 809.