International Journal of Scientific Research in Chemistry (IJSRCH) | ISSN : 2456-8457
© 2016 IJSRCH | Volume 1 | Issue 1

Synthesis and Characterizations of Triazine Derivative - N^2,N^4-bis(6-bromo-1,3-benzothiazol-2-yl)-N^6-aryl-1,3,5-triazine-2,4,6-triamine, derivative of 2,4,6-trimethyl-1,3,5-triazine as Biological Potent Agents

Hitendra N. Patel[1], Dr. B. B. Baldaniya[2]

[1]Department of Chemistry, Shri Jagdishprasad Jhabarmal Tibrewala University, Vidhyanagari, Jhunjhunu, Rajashthan, India

[2]Department of Chemistry, M. G. Science Institute, Navarangpura, Ahmedabad, Gujarat, India

ABSTRACT

A series of N^2,N^4-bis(6-bromo-1,3-benzothiazol-2-yl)-N^6-aryl-1,3,5-triazine-2,4,6-triamine 2a-k indole fused triazine derivatives have been synthesized by reaction between cyanuric chloride and benzothiazole. Product characterized by elemental and spectral analysis like IR and NMR.Further the compounds have been screened for antimicrobial activity against ten strains of Gram (+) and Gram (-) bacteria.

Keywords: Triazine, Antibacterial Activity.

I. INTRODUCTION

Antibacterial disease is very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. And therefore, it is an ongoing effort to synthesize new antimicrobial agents[1]. The quest for a more reliable and suitable drugs is always fascinating and challenging. A number of drugs containing simple heterocyclic or a combination of different moieties have been in use these days[2,31].

1,2,4-Triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities like A1 Adenosine receptor antagonists[3], Age-related macular degeneration[4], analgesic[5], anti-inflammatory activities[5], Anticancer Activity[6,7], anticonvulsant activity[8], antimicrobial activity[9,10], antinociceptive activity[11], Antiproliferativeactivity[12], anxioselective agent[13], Kinase inhibitor activity[14], Muscle Relaxant activity [15] .

An indole nucleus have arose great attention in recent years due to their wide variety of biological activities and pharmacological studies as cytotoxicity activity[16], Kinase inhibitors[17], anticancer[17], antiangiogenic agents[17], antimicrobial activity[18-21,23], Anti-HIV[22], anti-inflammatory[24], analgesic activity [24], Anticonvulsant activity[25,26] , Sedative-Hypnotic Activities[26] . Desai and co-workers[27] synthesized 2-(4-methoxy/2-methyl phenyl)-4-phenyl acetyl hydrazino-6-isonicotinyl hydrazino-s-triazines and tested them for their anti-HIV activity against susceptible human host cell (CEM cell line) over a wide range of concentrations. Based on the above observations, herein are reported the synthesis of various indole fused Triazine derivatives and evaluation of their antibacterial activity.

II. METHODS AND MATERIAL

Biological Activity

Antibacterial Activity

Antibacterial activity was carried out by TWO dilution method[28]. The strains used for the activity were secured from Institute of Microbial Technology. The compounds 2a-2k were observed for their antibacterial activity against Escherichia coli bacteria, Staphylocous aureus, Pseudomonas aeruginosa and Staphyloccous pyogenes at concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/mL respectively (Table 2).

Antifungal Activity

Same compounds are analyze for antifungal activity against *C. albicans A. niger and A. clavatus* at a concentrations of 100, 200, 500, and 1000 µg/mL respectively Table 2, for 2a-2k.The results are noted in the form of primary and secondary screening. Each synthesized drug was diluted to obtain 1000 µg/mL concentration, as a stock solution.

Experimental Section

Melting points are taken in open capillaries using paraffin. IR spectra were recorded on FTIR- Bruker spectrometer (V_{max} in cm^{-1}); Purity was checked by TLC using TLC aluminum sheets silica gel 60, supplied by E.Merck. The spots were located by keeping the plates in iodine vapor. 6-chloro-1,3-benzothiazol-2-amine was prepared by methods as described in literature[29-30].

For 2a compound: IR (kbr): 3454 (-N-H str., sec.amine), 3083(-C-H str., aromatic), 1527 (> C = N- str., ter. Amine), 1122 (C-S-C str., thiazol), 808 (disubstituted aromatic),1431 (C = N str., sec.amine).

NMR Spectra: 1H NMR spectra, were recorded in CDCl3 solution on a Bruker Avance DPX 200 MHz spectrometer Chemical shifts are reported as d (ppm) relative to TMS as internal standard.10.18δ (s, -NH, 2H), 9.34 δ (s, -NH, 1H), 8.54 δ (s, Ar-H, 8H).

Preparation of 6-chloro-N, N'-bis (6-bromo-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine:

In a conical flask, 2,4,6-trichloro-1,3,5-triazine (1) (0.01 mol) was taken acetone (20 ml) and 6-bromo-1,3-benzothiazol-2-amine (2) (0.02 mol) was added to it. To this mixture, 4% NaOH was added drop wise at room temperature. The solution was stirred for 4 h. The reaction mixture was poured onto crushed ice with constant stirring. The solution was neutralized with dil. HCl. The solid was filtered and washed with water. The product was recrystallized from acetone.; yield 76.00%.

Preparation of N^2,N^4-bis(6-bromo-1,3-benzothiazol-2-yl)-N^6-aryl-1,3,5-triazine-2,4,6-triamine :

In a round bottom flask, 6-chloro-N, N'-bis (6-bromo-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4-diamine. (3) (0.01 mol) and 1,4-dioxane (20 ml) was taken. To this mixture, aniline (0.01 mol) was added. The $p^H$was adjusted to neutral by adding 8% NaOH. The reaction mixture was refluxed for 2.5 h. And was poured onto crushed ice with constant stirring. The mixture was then neutralized with dil. HCl. The product was filtered and washed with cold water. The product was dried and recrystallized from methanol; Yield 65%

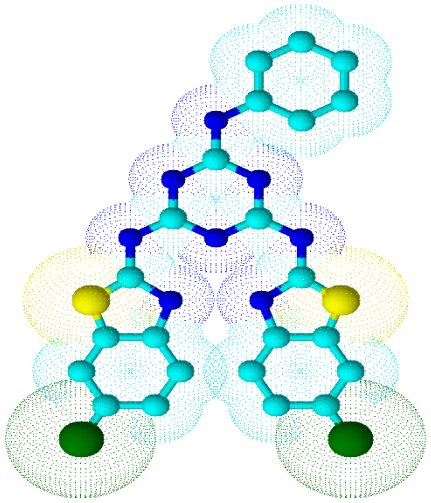

Figure 1. Structure of 2a

Scheme 1:

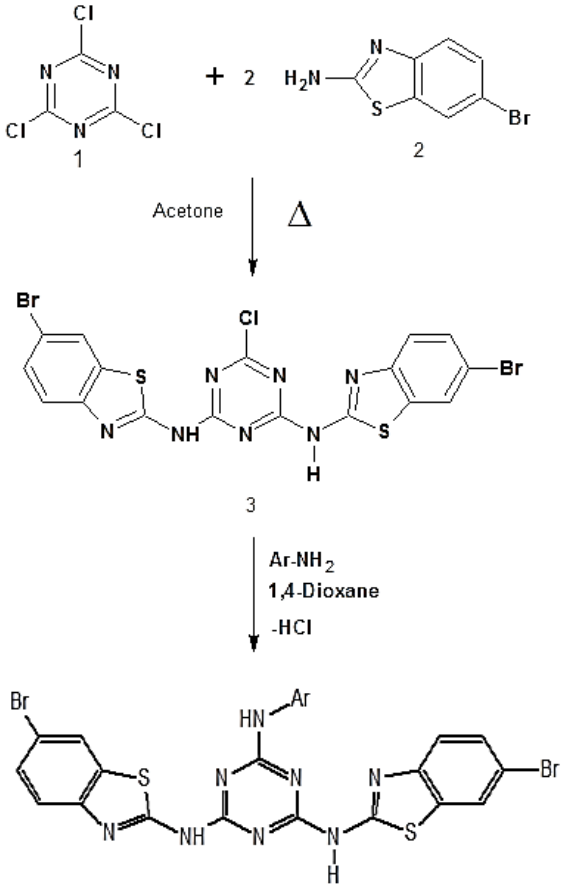

Figure 2. 2a-2k

Table I : Physical constant of the compounds (2a-2k)

Compd.	-Ar	Molecular Formula	m.p. (ºC)	Yield (%)	C (%) Found	C (%) Reqd.	N (%) Found	N (%) Reqd.
2a	$-C_6H_5$	$C_{23}H_{14}Br_2N_8S_2$	230	68	44.05	44.10	17.85	17.89
2b	$-3-Cl-C_6H_4$	$C_{23}H_{13}Br_2ClN_8S_2$	220	56	41.60	41.81	16.95	16.96
2c	$-4-Cl-C_6H_4$	$C_{23}H_{13}Br_2ClN_8S_2$	195	64	41.71	41.81	16.92	16.96
2d	$-3-NO_2-C_6H_4$	$C_{23}H_{13}Br_2N_9O_2S_2$	134	62	41.10	41.15	18.75	18.78
2e	$-4-NO_2-C_6H_4$	$C_{23}H_{13}Br_2N_9O_2S_2$	129	67	41.11	41.15	18.76	18.78
2f	$-4-Br-C_6H_4$	$C_{23}H_{13}Br_3N_8S_2$	220	58	39.15	39.17	15.84	15.89
2g	$-4-F-C_6H_4$	$C_{23}H_{13}Br_2FN_8S_2$	205	63	42.80	42.87	17.35	17.39
2h	$-2-C_5H_4N_2$	$C_{22}H_{13}Br_2N_9S_2$	215	64	42.10	42.12	20.04	20.09
2i	$-4-C_5H_4N_2$	$C_{22}H_{13}Br_2N_9S_2$	230	69	42.09	42.12	20.06	20.09
2j	$-N-CH_3-C_6H_4$	$C_{24}H_{16}Br_2N_8S_2$	215	58	45.00	45.01	17.49	17.50
2k	$-4-CH_3-C_6H_4$	$C_{24}H_{16}Br_2N_8S_2$	247	57	44.96	45.01	17.46	17.50

Table 2: Antibacterial and Antifungal Activities

SR NO.	Minimal Bactericidal Concentration (MBC) in µg/ml				Minimal Fungicidal Concentration (MFC) in µg/ml		
	E.coli	***P.aeruginosa***	***S.aureus***	***S.pyogenus***	***C.albicans***	***A.nigar***	***A.clavatus***
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	- 443	-1688	-96	- 442	-227	-282	-1323
2a	100	200	100	500	500	500	500
2b	100	100	500	500	200	200	200
2c	100	500	100	250	100	100	100
2d	100	100	500	500	100	100	100
2e	100	500	100	500	500	500	500
2f	250	500	100	250	100	100	100
2g	250	500	500	250	500	1000	1000
2h	500	100	100	500	500	500	500
2i	1000	1000	500	500	500	500	500
2j	100	100	500	500	200	200	200
2k	100	250	500	500	500	500	500

III. ACKNOWLEDGEMENT

The Author is thankful to the department of chemistry of JJT University, Rajasthan, North America Institute of Pharmaceutical Technology, Toronto and Department of chemistry, M. G. Science Institute, Ahmedabad for providing research and library facilities. The authors are also thankful to Department of chemistry, M. G. Science Institute for the IR analysis.

IV.REFERENCES

[1]. Solankee A, and Kapadia K Synthesis and studies of some novel s- triazine basedaminopyrimidines, isoxazoles and 1,5 benzothiazepines. Indian journal of chemistry, 2007; 46B:1707-1712.

[2]. **Baldaniya B. B.** and Patel P K, Synthesis Antibacterial and Antifungal Activities of s-Triazine Derivatives. E- Journal of Chemistry. 2009; 6(3): 673-680.

[3]. Settimo F.D. and Primofiore G. 3-Aryl [1, 2, 4] triazino [4, 3-a] benzimidazol-4(10H)-ones: A new class of selective A1 adenosine receptor antagonists. J. Med.Chem. 2001; 44, 316-327.

[4]. Palanki M. S. S. and Akiyama H. Development of prodrug 4-chloro-3-(5-methyl-3-{[4-(2-pyrrolidin-1-ylethoxy) phenyl] amino} 1, 2, 4-benzotriazin-7-yl) phenyl benzoate (TG!100801): A topically administered therapeutic candidate in clinical trials for the treatment of age-related macular degeneration. J. Med.Chem. 2008; 51, 1546-1559.

[5]. MakhloufAbdelmoneim A. and MakladYousreya A. Synthesis and analgesic- antiinflammatory activities of some 1, 2, 4-triazine derivatives, Arzneimittel-Forschung, 2004; 54(1): 42-49.

[6]. El-Gendy Z. and Morsy J. M. Synthesis of heterobicyclic nitrogen systems bearing a 1,2,4-triazine moiety as anticancer drugs: part iv. Phosphorus, Sulfur, and Silicon, 2003; 178: 2055–2071.

[7]. Sztanke K. and Pasternak K. Synthesis, structure elucidation and identification of antitumoural properties of novel fused 1,2,4-triazine aryl derivatives. Europ. J. of medi. Chem, 2008; 43: 1085-1094.

[8]. Mallikarjuna B. P. and Suresh Kumar G. V. Synthesis and anticonvulsant activity of some potent 5,6-bis aryl 1,2,4-triazines. J. Zhejiang UnivSci B. 2007; 8(7): 526-532.

[9]. Sztanke K. and Pasternak K. Antibacterial action of novel 8-aryl-4-imino- 2, 3, 7, 8-tetrahydroimidazo [2,1-c][1, 2, 4] triazin- 3 (6H)-one derivatives. AnnalesUniversitatismariaecurie - S k łodowska Lublin – Polonia. 2007; LXII.

[10]. Modzelewska-Banachiewicz B. and Kowalski C. Biological activity of 1,2,4-triazineand 1,2,4-triazole derivatives., Annalesuniversitatismariae curie - skłodowskalublin – polonia. 2007;LXII.

[11]. Sztanke K. and Fidecka S. Antinociceptive activity of new imidazolidine carbonyl derivatives. Part 4. synthesis and pharmacological activity of 8-aryl-3,4-dioxo-2H,8H-6,7-dihydroimidazo[2,1-c][1,2,4]triazines. Europ. J. of Medi. Chem. 2005; 40: 127–134.

[12]. Diana P. and Barraja P. Pyrrolo[2,1-c][1,2,4]triazines from 2-diazopyrroles: synthesis and antiproliferative activity. Europ. J. Medi.Chem. 2002; 37: 267–272.

[13]. Costanzo A, Guerrini G, Benzodiazepine receptor ligands.7. Synthesis and pharmacological evaluation of new 3-esters of the 8-chloropyrazolo[5,1-c] [1,2,4]benzotriazine 5-oxide. 3-(2- Thienylmethoxycarbonyl) derivative: an anxioselective agent in rodents., Journal Med Chem., 2002, 45(26), 5710-20.

[14]. Hunt J T and Mitt T, Discovery of the pyrrolo[2,1-f][1,2,4]Triazine nucleus as a new Kinase inhibitor template., Journal Med.Chem., 2004, 47, 4054-4059.

[15]. Costanzo A and Guerrini G, Benzodiazepine Receptor Ligands. 4. synthesis and pharmacological evaluation of 3-heteroaryl-8-chloropyrazolo[5,1-c][1,2,4]benzotriazine 5-oxides., Journal Med.Chem., 1999, 42, 2218-2226.

[16]. Hoque M. M. and Islam M. R. Cytotoxicity study of some indophenines and isatin derivatives. Bangladesh J. Pharmacol. 2008;3: 21-26.

[17]. Abadi A. H. and Abou-Seri S. M. Synthesis of 3-substituted-2 oxoindole analogues and their evaluation as kinase inhibitors, anticancer and antiangiogenic agents. Europ. J. Medi. Chem. 2006; 41: 296–305.

[18]. George S. and Parameswaran M. K. Synthesis and evaluation of the biological activities of some 3-{[5-(6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-oxadiazol-2-yl]-imino}-1,3-dihydro-2H-indol-2-one derivatives. Acta Pharm. 2008; 58: 119–129.

[19]. Ravichandran V. and Mohan S. Synthesis and antimicrobial activity of Mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl)amino]phenyl acetic acid. Arkivoc. 2007; 14: 51-57.

[20]. Aanandhi M. V. and George S. Synthesis and antimicrobial activities of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted pyridin-2-yl)thiosemicarbazide. Arkivoc. 2008; 9; 187-194.

[21]. Patel A. and Sanjay Bari S., Synthesis and Antimicrobial Activity of Some New Isatin Derivatives. Indian J. Pharm. Research. 2006; 4:249-254.

[22]. Sriram D. and Bal T. R. Aminopyrimidiniminoisatin analogues: Design of novel nonnucleoside HIV-1 reverse transcriptase inhibitors with broadspectrum Chemotherapeutic properties. J. Pharm. Pharmaceut. Sci. 2005; 8(3):565-577.

[23]. Jarrahpour A. and Khalili D. Synthesis, Antibacterial, Antifungal and Antiviral Activity Evaluation of Some New bis-Schiff Bases of Isatin and Their Derivatives. Molecules. 2007: 12: 1720-1730.

[24]. Muthukumar V. A. and George S. Synthesis and Pharmacological Evaluation of 1-(1-((Substituted)methyl)-5-methyl-2-oxoindolin-3-ylidene)-4-(substitutedpyridin-2-yl) thiosemicarbazide. Biol. Pharm.Bull. 2008; 31(7): 1461-1464.

[25]. Verma M. and Pandeya S. N. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm. 2004; 54: 49–56.

[26]. Smitha S. and Pandeya S. N. Anticonvulsant and Sedative-Hypnotic Activities of N-Acetyl / Methyl Isatin Derivatives. Sci. Pharm. 2008; 76: 621–636.

[27]. Desai N.C., Parikh A.R.; Indian J Exptl Biol.; 34, 584-587, 1996.

[28]. National Committee for Clinical Laboratory Standard. Reference method for broth dilution antifungal susceptibility testing of yeasts Approved standard M27A. 1997, NCCLS, Wayne, PA.

[29]. Organic synthesis; Collective vol.3; Noland, Wayland E., Editor in-chief; John Wiley & Sons. Inc. New York, 76, 1962.

[30]. Desai N C, Dipika Dave, Shah M.D.and Vyas G.D., Indian J Chem, 39B, 2000, 277.

[31]. Baldaniya B. B., Synthesis and Characterizations of N 2 -(Aryl)-N 4 , N 6 -bis (6, 7-dichloro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4, 6-triamines as Biological Potent Agents. E- Journal of Chemistry. 2010, 7(1), 210-214.