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Synthesis and Characterization of Biologically Significant 3-(2-Oxo-1,2,dihydroindol-3-ylideneamino)-3H-benzo[d][1,2,3]triazin-4-ones

G. SAMMAIAH and M. SARANGAPANI*
Medicinal Chemistry Laboratory, University College of Pharmaceutical Sciences
Kakatiya University, Warangal-506 009, India
E-mail: mandasarangapani@yahoo.co.in

In the present work, some new 3-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-3H-benzo[d][1,2,3]triazin-4-ones, were prepared. 2-Amino benzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene)hydrazides (**1**), on cyclization with sodium nitrite in presence of glacial acetic acid afforded 3-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-3H-benzo[d][1,2,3]-triazin-4-ones (**2**). The structures of the products were characterized by IR spectral study. All the compounds were evaluated for anticancer, antioxidant and antimicrobial activities. Some of these compounds showed good anti-cancer activity (against HeLa Cell lines, IMR-32 cell lines), antioxidant, antibacterial and antifungal activities.

Key Words: Synthesis, Biological activity, 3-(2-Oxo-1,2-dihydroindol-3-ylideneamino)-3H-benzo[d][1,2,3]triazin-4-ones.

INTRODUCTION

Jiang *et al.*[1-4] reported the synthesis and cytotoxic activity of some novel 3-amino-1,2,4-benzotriazin-1,4-dioxide derivatives. In the last few years, benzotriazinone derivatives have been discovered which show potential local anaeshtetic activity[5], cytotoxicity[6] and act as selective ligands with good affinity for human melanin-concentrating hormone receptor[7].

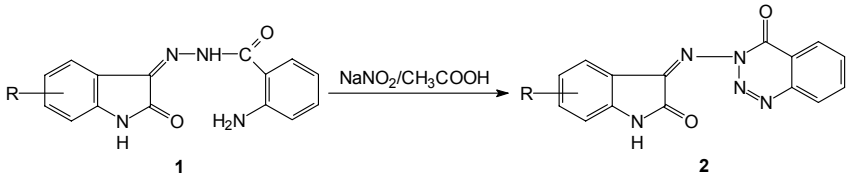
In present communication, the synthesis and characterization of some new 3-(2-oxo-1,2-dihydro-indol-3-ylideneamino)-3H-benzo[d][1,2,3]-triazin-4-ones are reported. 2-Amino benzoic acid (2-oxo-1,2-dihydro-indol-3-ylidene) hydrazides (**1**) on cyclization with sodium nitrite in presence of glacial acetic acid yielded 3-(2-oxo-1,2-dihydroindol-3-ylideneamino)-3H-benzo[d] [1,2,3]triazin-4-ones (**2**). All the compounds of the series were screened for anticancer, antioxidant, antibacterial and anti-fungal activities. The structures of these compounds were identified by IR, NMR and mass spectra.

EXPERIMENTAL

Synthesis of 3-(2-oxo-1,2-dihydroindol-3-ylideneamino)-3H-benzo[d]-[1,2,3]triazin-4-ones (2)

Each of the 2-amino benzoic acid (2-oxo-1,2-dihydroindol-3-ylidene)-hydrazide (**1**, 0.001 mol) was dissolved in acetic acid (10 mL), added slowly the solution of sodium nitrite (0.001 mol) at 0 ºC. The reaction mixture was stirred well and kept aside for 24 h. The product thus separated was filtered, washed thoroughly with cold water and dried (**Scheme-I**).

Adopting this procedure, 15 compounds were synthesized and their melting points were determined in open capillary tubes using Toshniwal melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC.



1 2

Scheme-I

RESULTS AND DISCUSSION

The synthesized compounds were characterized by the spectral data IR, PMR and mass spectra. The yields, melting points and physical data are shown in Table-1.

Compound **2a:** IR (KBr, cm^{-1}) 3325 ν(NH), 1742 ν(C=O), 1550 ν(C=N). ^{1}H NMR (DMSO-d_6, δ ppm) 11.17 (S, 1H, NH lactam), 6.95-8.33 (m, 8H, Ar-H). Mass (M+1) peak at m/z 291.

Compound **2b:** 11.05 (S, 1H, NH lactam), 6.82-8.3 (m, 7H, Ar-H), 2.5 (S, 3H, CH_3). Mass (M+1) at m/z 305.

Antibacterial activity[8]: Table-1 pertaining to the antibacterial data of 3-(2-oxo-1,2-dihydroindol-3-ylideneamino)-3H-benzo[d][1,2,3]triazin-4-ones indicates that few of the compounds exhibited antibacterial activity (cup plate method). Compound **2h** (R=7-Cl) was specifically active only against gram-negative organisms *Kl. aeruginosa* and *E. coli* with zone of inhibition of 5.28 and 3.84 mm, respectively. Compounds **2a** (R=H) and **2d** (R=NO_2) exhibited activity against only *E. coli*, whereas compounds **2e** (5-COOH), **2g** (5-Br), **2i** (7-CH_3) and **2j** (6-Br) did not show any activity against any of the test organisms employed.

Antifungal activity[9]: The data on antifungal activity (cup plate method) of 3-(2-oxo-1,2-dihydroindol-3-ylideneamino)-3H-benzo[d][1,2,3]triazin -4-ones presented in Table-1 reveals that some of the compounds of this

TABLE-1
CHARACTERIZATION DATA OF 3-(2-OXO-1, 2, DIHYDRO-INDOL-3-YLIDENEAMINO)-3H-BENZO [d][1,2,3]-TRIAZIN-4-ONES (**2a-o**)

Compd.	R	m.p. (ºC) [Yield (%)]	m.f. [m.w.]	Antimicrobial activity					
				KA	EC	BS	SA	CA	AN
2a	H	246 [90]	$C_{15}H_9N_5O_2$ [291]	-	1.12	-	-	-	0.8
2b	5-CH_3	250 [88]	$C_{16}H_{11}N_5O_2$ [305]	-	1.12	1.12	3.76	0.92	1.2
2c	5-Cl	256 [78]	$C_{15}H_8N_5O_2Cl$ [325]	-	2.28	1.2	1.84	0.24	1.1
2d	5-NO_2	246 [70]	$C_{15}H_8N_6O_4$ [336]	-	5.88	-	-	-	-
2e	5-COOH	232 [50]	$C_{16}H_9N_5O_4$ [335]	-	-	-	-	-	-
2f	7-$COOCH_3$	244 [75]	$C_{17}H_{11}N_5O_4$ [349]	3.6	1.6	-	1.62	-	-
2g	5-Br	250 [95]	$C_{15}H_8N_5O_2Br$ [370]	-	-	-	-	0.54	0.96
2h	7-Cl	252 [60]	$C_{15}H_8N_5O_2Cl$ [325]	5.28	3.84	-	-	-	-
2i	7-CH_3	242 [80]	$C_{16}H_{11}N_5O_2$ [305]	-	-	-	-	0.31	-
2j	6-Br	245 [90]	$C_{15}H_8N_5O_2Br$ [370]	-	-	-	-	0.36	0.88
2k	5-I	260 [60]	$C_{15}H_8N_5O_2I$ [411]	1.28	0.92	3.28	2.08	1.3	1.4
2l	5-F	241 [90]	$C_{15}H_8N_5O_2F$ [307]	0.64	-	-	3.04	0.64	1.1
2m	5-$COOCH_3$	240 [64]	$C_{17}H_{11}N_5O_2$ [449]	2.2	-	-	1.6	-	-
2n	4-Cl.5-F	239 [85]	$C_{15}H_7N_5O_2FCl$ [343]	3.2	-	-	2.01	0.96	1.3
2o	7-NO_2	240 [65]	$C_{15}H_8N_6O_4$ [336]	1.3	-	1.28	-	-	-
Std.	Ampicillin	(10 µg/cup)		10	10	8	12	-	-
Std.	Griseofulvin	(10 µg/cup)		-	-	-	-	1	1.5

KA = *Kl. aeruginosa*; EC = *E. coli*; BS = *B. stereothermophilus*; SA = *S. aureus*; CA = *C. albicans* and AN = *A. niger*
Concentration of the test compounds; 10 µg/cup

series exhibited antifungal activity against two strains of fungi employed. Amongst them, compound **2k** (R = 5-I) and **2n** (R = 4-Cl, 5-F) were found to be comparatively more effective antifungal compounds. The activity is comparable with the standard griseofulvin.

Anticancer activity[10-13]: The data on IC_{50} values of anticancer activity of the compounds was assayed by Microculture tetrazolium assay (MTT) is based on the metabolic reduction of 3-(4,5-dimethylthiazol-2,5-diphenyl)tetrazolium bromide (MTT) to water insoluble formazan crystals with mitochondrial dehydrogenase enzyme, which gives direct correlation of viable cells. Anticancer activity of 3-(2-oxo-1,2-dihydroindol-3-ylidene amino)-3H-benzo[d][1,2,3]triazin-4-ones is given in the Table-2. The activity in IC_{50} value is ranging from 210 to 515 mM. The compound **2k** (R = 5-I) showed highest anticancer activity among the series at a concentration of 210 mM against HeLa cell lines. This was followed by the compound **2j** (R = 6-Br) and **2g** (R =5-Br) with IC_{50} of 245, 246 and 281.1 mM, 407 mM, respectively against HeLa and IMR-32 cell lines. The compounds **2e**, **2i**, **2l** and **2m** did not shown any activity against HeLa cell lines and IMR-32 cell lines.

TABLE-2
ANTICANCER AND ANTIOXIDANT ACTIVITIES OF 3-(2-OXO-1,2-DIHYDRO-INDOL-3-YLIDENEAMINO)-3H-BENZO[d][1,2,3]-TRIAZIN-4-ONES(**2**)

Compd.	R	HeLa cell lines	IMR-32 cell lines	Antioxidant activity
		IC_{50} value (μM)	IC_{50} value (μM)	IC_{50} value (μM)
2a	H	325	515.00	13.54
2b	5-CH_3	305	295.00	15.34
2c	5-Cl	385	307.00	10.63
2d	5-NO_2	413	NA	11.67
2e	5-COOH	NA	NA	21.36
2f	7-$COOCH_3$	415	NA	23.54
2g	5-Br	246	407.00	11.35
2h	7-Cl	359	NA	13.65
2i	7-CH_3	NA	NA	24.98
2j	6-Br	245	281.20	13.68
2k	5-I	210	NA	19.67
2l	5-F	NA	NA	24.36
2m	5-$COOCH_3$	NA	NA	21.96
2n	4-Cl.5-F	465	NA	19.67
2o	7-NO_2	368	NA	25.64
Cisplatin		20.00	20.00	-
Ascorbic acid		-	-	6.54

Antioxidant activity[14-18]: Antioxidat activity of the compounds was evaluated by DPPH method and the data is presented in Table-2. Among these compounds, compound **2c** (R=5-Cl) showed highest percentage of free radical scavenging activity (10.63 mM). Compound **2a** (R = H), **2d** (R = 5-NO_2), **2g** (R = 5-Br) and **2j** (R=6-Br) showed activity with IC_{50} values of 13.54, 11.67 11.35 and 13.68 mM, respectively whereas the rest of the

compounds showed mild antioxidant activity with IC_{50} values in the range 15.34 to 25.64 mM.

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