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SYNTHESIS OF 1,2,4-TRIAZINE DERIVATIVES AS POTENTIAL ANTI-ANXIETY AND ANTI-INFLAMMATORY AGENTS

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Abstract: A series of 1,2,4-triazine derivatives **Va** (**1**-**24**) and **Vb** (**1**-**24**) were synthesized and evaluated for their anti-anxiety and anti-inflammatory activities. The structures of the synthesized compounds were confirmed on the basis of their spectral data. Many of the triazine compounds were found to possess good activity. Especially, compounds bearing the sulfur atom showed better activity than those bearing the oxygen atom.

Keywords: 1,2,4-triazines, anti-anxiety, anti-inflammatory.

"Anxiety" is a cardinal symptom of many psychiatric disorders and is commonly associated with depression, especially with dysthymic disorder, panic disorder, agoraphobia and other specific phobias like obsessive-impulsive disorder, eating disorder and many personality disorders (1, 2). The success of pharmacological treatments for these disorders has been obstructed by various factors, including resistance to treatment and adverse effects of the drugs used. Current anxiolytic drugs are based on pharmacological interactions with classic transmitters (3).

1,2,4-Triazine derivatives have been reported to possess a broad spectrum of biological activities, including antifungal (4, 5), anti-HIV (6), anticancer (7), anti-inflammatory (8), analgesic (9) and antihypertensive activities (10). Besides this, triazines were used as herbicides, pesticides and dyes (11, 12). This prompted us to synthesize hydrazones derivatives of 1,2,4-triazines and evaluate them for anti-anxiety and anti-inflammatory activities.

EXPERIMENTAL

All the solvents were of LR grade and obtained from Merck, CDH (Germany) and SD-Fine Chemicals (India). Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed on silica gel G (Merck). All the reactions were monitored using benzene: acetone (4 : 1, v/v) as a solvent system.

The FT-IR spectra were recorded in KBr pellets on a (BIO-RAD) WIN-IR Spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker model (300 MHz) FT-NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a Jeol JMS-D instrument fitted with a JMS 2000 data system at 70 eV (Tables 1-3). The animal experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC).

Anti-anxiety screening

Two phase screening was performed on mice to screen out the test compounds. In phase I, all the test compounds were evaluated by Forced Swimming Test (FST) model. The FST is a well known screening model for antidepressant developed by Porsolt et al. (13, 14) in which immobility was determined. In phase II, the compounds with different substituents having different electronegativity were further evaluated by Avoidance Exploratory Behavior test (15) in which transitions were determined.

In both the phases diazepam was used as a reference substance. Both reference and test compounds were administered orally at a dose of 4

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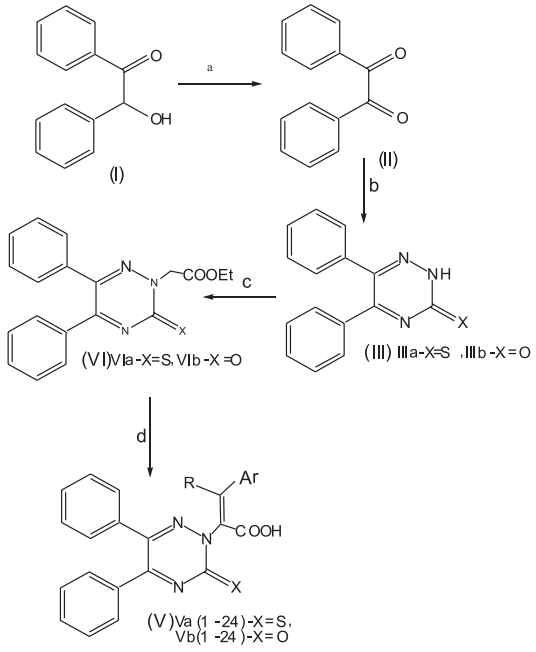

Scheme 1. (a) conc. HNO_3, (b) thiosemicarbazide/semicarbazide, acetic acid, (c) $ClCH_2COOEt$, pyridine, (d) substituted aldehydes/acetophenones

mg/kg body weight. Data are presented in Tables 3 and 4.

Anti-inflammatory screening (Table 6)

The *in-vivo* anti-inflammatory activity was carried out by Winter et al. method (16) in which paw inflammation in albino rats was induced by carrageenan in a hind paw of rat and the edema volume was measured using Ugo Basile plethysmometer. Indomethacin at a dose of 20 mg/kg body weight was used as a reference drug.

Synthesis of benzil (II)

Benzoin (**I**) (20 g, 0.094 mol) and 100 mL conc. HNO_3 was taken in a 250 mL round bottom flask and heated on a boiling water bath with occasional shaking until the evolution of oxides of nitrogen seized. The reaction mixture was then poured onto crushed ice, stirred well till the yellow solid separated out. It was filtered out and recrystallized from ethanol to yield benzil (**II**). The obtained substance was identical with commercial one.

General method for synthesis of III

0.05 mol of benzil (**II**) and equimolar amount of either thiosemicarbazide or semicarbazide were dissolved in 30 mL of acetic acid. The reaction mixture was then refluxed for 8-10 h. After the completion of reaction, the reaction mixture was poured onto the crushed ice. The solid mass precipitated was filtered, washed with water, and recrystallized from ethanol to yield compounds **IIIa** or **IIIb**, respectively.

5,6-Diphenyl-1,2,4-triazine-3(2H)-thioxo (**IIIa**)

M.p. 160-165°C, yield 85%, IR (KBr, cm^{-1}): 3157 (N-H), 1675 (C=N), 1527 (C=S), ^{1}H NMR (DMSO-d_6, δ, ppm): 7.28-7.42 (m, 10H, ArH), 8.02 (s, 1H, NH).

5,6-Diphenyl-1,2,4-triazine-3(2H)-one (**IIIb**)

M.p.- 170-172°C, yield 84%, IR (KBr, cm^{-1}): 3157 (N-H), 1675 (C=N), 1637 (C=O), ^{1}H NMR (DMSO-d_6, δ, ppm): 7.34-7.63 (m, 10H, ArH), 8.10 (s, 1H, NH).

General method for synthesis of IV

Compound **IIIa/IIIb** (0.056 mol) was dissolved in pyridine (30 mL) and the solution was chilled on an ice bath. Chloroethylacetate (0.112 mol) was added dropwise with constant shaking and the mixture was further stirred for 0.5 h and poured into ice cold water. The solid separated out was filtered and washed with water. The product **IVa/IVb** was recrystallized from ethanol.

Ethyl (5,6-diphenyl-3-thioxo-1,2,4-triazine-2(3H)-yl)acetate (**IVa**)

M.p. 135-138°C, yield 80%, IR (KBr, cm^{-1}): 2983 (C-H, alkane), 1731 (C=O), 1608 (C=N), 1526 (C=S), 1341 (C-N), ^{1}H NMR (DMSO-d_6, δ, ppm): 7.82-7.96 (m, 10H, ArH), 3.64 (q, 2H, CH_2), 2.96 (s, 2H, -CH_2CO), 2.23 (t, 3H, CH_3).

Ethyl (5,6-diphenyl-3-oxo-1,2,4-triazine-2(3H)-yl)acetate (**IVb**)

M.p. 142-145°C, yield 80%. IR (KBr, cm^{-1}): 2998 (C-H, alkane), 1731 (C=O), 1596 (C=N), 1373 (C-N), ^{1}H NMR (DMSO-d_6, δ, ppm): 7.85-7.97 (m, 10H, ArH), 3.93 (q, 2H, CH_2), 3.04 (s, 2H, -CH_2CO), 2.27 (t, 3H, CH_3).

General method for synthesis of V

An equimolar amount of compound **IVa/IVb** (0.014 mol) and differently substituted aldehydes/acetophenones in methanol (20 mL) were taken in a flask. To this, 40% w/v methanolic KOH solution (3 mL) was added and stirred for 2 h then left overnight. The mixture was poured onto crushed ice, filtered, washed, dried and recrystallized from ethanol to yield corresponding final products: 2-(5,6-diphenyl-3-thioxo-1,2,4-triazine-2-yl)-3-substituted-acrylic acid (**Va$_{(1-24)}$**) and 2-(5,6-diphenyl-3-oxo-1,2,4-triazine-2-yl)-3-substituted-acrylic acid (**Vb$_{(1-24)}$**) (Tables 1-3).

Table. 1 Characterization of test compounds **Va**

Compd. **Va**	R	Ar	M.p. (°C)	% yield	IR (KBr, cm^{-1})	^{1}H NMR (DMSO-d_6, δ, ppm)
1	H	2-OH-C_6H_4	207-210	74	3650 (O-H), 3062 (C-H, Ar), 1675 (C=O), 1584 (C=S)	13.34 (bs, 1H, COOH), 9.03 (s, 1H, OH), 7.20-7.82 (m, 14H, ArH), 6.85 (s, 1H, CH)
2	H	3-OH-C_6H_4	212-215	80	3475 (O-H), 3062 (C-H,Ar), 1665(C=O), 1527(C=S), 1398 (C-O), 1348 (C-N)	11.564 (s, 1H, COOH), 9.01 (s, 1H, OH), 7.30-7.79 (m, 14H, ArH) , 6.842 (s, 1H, CH)
3	H	4-OH-C_6H_4	220-225	76	3546 (O-H), 3062 (C=C, Ar),1694 (C=O), 1564 (C=S)	12.92 (bs, 1H, COOH), 9.21 (s, 1H, OH), 7.20-7.77 (m, 14H, ArH), 6.88 (s, 1H, CH)
4	H	3,4-$(OH)_2$-C_6H_3	222-228	78	3536 (O-H), 3103 (C=C, Ar), 1627 (C=O), 1556 (C=S)	11.92 (bs, 1H, COOH), 9.45 (s, 2H, OH), 7.45-7.87 (m, 13H, ArH), 6.43 (s, 1H, CH)
5	H	4-Cl-C_6H_4	253-257	68	1753 (C=O), 1626 (C=N), 1559 (C=S), 725 (C-Cl)	12.20 (bs, 1H, COOH), 7.56-7.97 (m, 14H, ArH), 6.87 (s, 1H, CH)
6	H	2-Cl-C_6H_4	235-239	71	1703 (C=O), 1657 (C=N), 1529 (C=S), 720 (C-Cl)	12.34 (bs, 1H, COOH), 7.20-7.71 (m, 14H, ArH), 6.85 (s, 1H, CH)
7	H	2,4-$(Cl)_2$-C_6H_3	240-243	74	3640 (O-H), 3067 (C-H), 1699 (C=O), 1584 (C=S), 1307 (C-N), 722(C-Cl)	10.23 (bs, 1H, COOH), 7.45-7.75 (m, 14H, ArH), 6.67 (s, 1H, CH)
8	H	4-OCH_3-C_6H_4	225-230	78	3491 (OH), 3070 (CH, Ar), 1677 (C=O), 1601 (C=N), 1528 (C=S), 1350 (C-N)	11.25 (s, 1H, COOH), 7.39-7.67 (m, 14H, ArH), 6.89 (s, 1H, CH),4.02 (s, 3H, OCH_3)
9	H	3,4,5-$(OCH_3)_3$-C_6H_2	238-240	71	3765 (OH), 1597 (C=O), 1508 (C=S)	12.02 (s, 1H, COOH), 7.49-7.78 (m, 12H, ArH), 6.89 (s, 1H, CH), 4.13 (s, 9H, OCH_3)
10	H	3,4-$(OCH_3)_2$-C_6H_3	230-233	73	3735 (OH), 1686 (C=O), 1528 (C=S)	11.73 (s, 1H, COOH), 7.19-7.60 (m, 13H, ArH), 6.89 (s, 1H, CH), 3.94 (s, 6H, OCH_3)
11	H	2-OH,3-CH_3-C_6H_3	265-268	74	3528 (OH), 1586 (C=O), 1612 (C=S)	12.52 (s, 1H, COOH), 9.86 (s, 1H, OH), 7.49-7.90 (m, 13H, ArH), 6.89 (s, 1H, CH), 3.67 (s, 3H, OCH_3)
12	H	4-Br-C_6H_4	242-247	70	3651 (OH), 3060 (CH), 1530 (C=S)	12.09 (bs, 1H ,COOH), 7.45-7.85 (m, 14H, ArH), 6.82 (s, 1H, CH)
13	H	4-$N(CH_3)_2$-C_6H_5	228-230	78	3634 (OH), 1701 (C=O), 1637 (C-N), 1566 (C=S)	10.73 (s, 1H, COOH), 7.36-7.70 (m, 15H, ArH), 6.69 (s, 1H, CH), 1.67 (s, 6H, CH_3)
14	H	CH=CH-C_6H_5	226-230	80	3649 (OH), 1596 (C=O), 1565 (C=S)	11.43 (s, 1H, COOH), 7.59-7.87 (m, 17H, ArH+CH=CH), 6.85 (s, 1H, CH)
15	H	Indole	238-240	75	3540 (OH), 3230 (NH), 3068 (CH), 1720 (C=O)1528 (C=S)	10.12 (s, 1H, COOH), 7.40-7.55 (m, 15 H, ArH), 6.89 (s,1 H, NH), 6.68 (s, 1H, CH)
16	H	Furan	214-218	68	3490 (OH), 3049 (CH), 1738 (C=O), 1530 (C=S)	10.64 (s, 1H, COOH), 7.56-7.75 (m, 14H, ArH), 6.80 (s, 1H, CH)
17	H	-C_6H_5	202-205	78	3734 (OH), 1683 (C=O), 1607 (C=N) ,1526 (C=S)	12.09 (s, 1H, COOH), 7.43-7.73 (m, 15H, ArH), 6.84 (s, 1H, CH)
18	CH_3	4-Br-C_6H_4	255-258	76	3642 (OH), 3060 (CH, Ar), 1673 (C=O),	1661 (C=N) 12.09 (s, 1H, COOH), 7.22-7.85 (m, 14H, ArH), 2.71(s, 3H, CH_3)
19	CH_3	4-CH_3-C_6H_4	272-275	79	3867 (OH), 1657 (C=O), 1565 (C=S)	11.99 (s, 1H, COOH), 7.32-7.85 (m, 14H, ArH), 3.05 (s, 3H, CH_3), 2.31 (s, 3H, CH_3)
20	CH_3	3,4-$(OH)_2$- C_6H_4	240-244	65	3547 (OH), 1577 (C=O), 1595 (C=S)	12.39 (s, 1H, COOH), 9.47 (s, 2H, OH), 7.42-7.88 (m, 14H, ArH), 2.94 (s, 3H, CH_3)
21	CH_3	4-NO_2-C_6H_4	228-230	65	3342 (OH), 1680 (C=O), 1530 (C=S), 1348 (N-O)	12.23 (s, 1H, COOH), 7.32-7.82 (m, 14H, ArH), 2.74 (s, 3H, CH_3)
22	CH_3	4-OH-C_6H_4	260-263	68	3538 (OH), 3078 (CH, Ar), 1718 (C=O), 1538 (C=S)	12.09 (s, 1H, COOH), 9.40 (s, 1H, OH), 7.50-7.88 (m, 14H, ArH), 2.92 (s, 3H, CH_3)
23	CH_3	4-OCH_3-C_6H_4	234-238	64	3442 (OH), 1680 (C=O), 1530 (C=S), 1225 (C-O)	12.33 (s, 1H, COOH), 7.32-7.82 (m, 14H, ArH), 3.67 (s, 3H, OCH_3), 2.14 (s, 3H, CH_3)
24	CH_3	2-OH-C_6H_4	254-260	62	3546 (OH), 1750 (C=O), 1530 (C=S)	11.39 (s, 1H, COOH), 8.97 (s, 1H, OH), 7.35-7.78 (m, 14H, ArH), 2.62 (s, 3H, CH_3)

Table 2. Characterization of test compounds **Vb**

Compd. **Va**	R	Ar	M.p. (°C)	% yield	IR (KBr, cm^{-1})	^1H NMR (DMSO-d_6, δ, ppm)
1	H	2-OH-C_6H_4	213-216	72	3649 (O-H), 3053 (C-H, Ar), 1655 (C=O)	12.42 (bs, 1H, COOH), 8.93 (s, 1H, OH), 7.24-7.83 (m, 14H, ArH), 6.85 (s, 1H, CH)
2	H	3-OH-C_6H_4	256-260	70	3525 (O-H), 3131 (C-H, Ar), 1655 (C=O), 1398 (C-O), 1371 (C-N)	11.54 (s, 1H, COOH), 9.1 (s, 1H, OH), 7.38-7.77 (m, 14H, ArH), 6.52 (s, 1H, CH)
3	H	4-OH-C_6H_4	250-255	74	3506 (O-H), 3049 (C=C, Ar), 1651 (C=O)	12.92 (bs, 1H, COOH), 9.21 (s, 1H, OH), 7.20-7.77 (m, 14H, ArH), 6.88 (s, 1H, CH)
4	H	3,4-$(OH)_2$-C_6H_3	263-265	54	3556 (O-H), 3174 (C=C, Ar), 1673 (C=O)	11.92(bs,1H,COOH), 9.45(s,2H,OH), 7.45-7.87(m,13H,ArH) ,6.43(s,1H,CH)
5	H	4-Cl-C_6H_4	219-222	68	1773 (C=O), 1651 (C=N), 728 (C-Cl)	12.19 (bs, 1H, COOH), 7.36-7.67 (m, 14H, ArH), 6.87 (s, 1H, CH)
6	H	2-Cl-C_6H_4	265-270	52	1717 (C=O), 1697 (C=N), 720 (C-Cl)	12.34 (bs, 1H, COOH), 7.20-7.71 (m, 14H, ArH), 6.58 (s, 1H, CH)
7	H	2,4-$(Cl)_2$-C_6H_3	203-206	76	3673 (O-H), 3057 (C-H), 1674 (C=O), 1305 (C-N), 722 (C-Cl)	11.23 (bs, 1H, COOH), 7.32-7.70 (m, 14H, ArH), 6.97 (s, 1H, CH)
8	H	4-OCH_3-C_6H_4	251-255	78	3491 (OH), 3070 (CH, Ar), 1677 (C=O), 1601 (C=N), 1350 (C-N)	10.25 (s, 1H, COOH), 7.39-7.67 (m, 14H, ArH), 6.09 (s, 1H, CH), 3.62 (s, 3H, OCH_3)
9	H	3,4,5-$(OCH_3)_3$-C_6H_2	285-288	58	3796 (OH),1579(C=O)	11.93 (s, 1H, COOH), 7.29-7.81 (m, 12H, ArH), 6.59 (s, 1H, CH), 4.03 (s, 9H, OCH_3)
10	H	3,4-$(OCH_3)_2$-C_6H_3	280-283	67	3775 (OH), 1674 (C=O)	11.74 (s, 1H, COOH), 7.19-7.60 (m, 13H, ArH), 6.79 (s, 1H, CH), 3.94 (s, 6H, OCH_3)
11	H	2-OH,3-OCH_3-C_6H_3	279-282	63	3528 (OH), 1586 (C=O)	11.52 (s, 1H, COOH), 9.63 (s, 1H, OH), 7.49-7.90 (m, 13H, ArH), 6.89 (s, 1H, CH), 3.27 (s, 3H, OCH_3)
12	H	4-Br-C_6H_4	203-205	62	3651 (OH), 3060 (CH)	12.09 (bs, 1H, COOH), 7.45-7.85 (m, 14H, ArH), 6.82 (s, 1H, CH)
13	H	4N$(CH_3)_2$-C_6H_5	199-205	69	3634 (OH), 1701 (C=O), 1637 (C-N)	11.73 (s, 1H, COOH), 7.36-7.70 (m, 15H, ArH), 6.59 (s, 1H, CH), 1.42 (s, 6H, CH_3)
14	H	CH=CH-C_6H_5	210-212	70	3649(OH),1596(C=O)	11.43 (s, 1H, COOH), 7.59-7.87 (m, 17H, ArH + CH=CH), 6.85 (s, 1H, CH)
15	H	Indole	262-265	61	3540 (OH), 3230 (NH), 3068 (CH), 1720 (C=O)	10.12 (s, 1H, COOH), 7.40-7.55 (m, 15H, ArH), 6.89 (s, 1H, NH), 6.68 (s, 1H, CH)
16	H	Furan	222-225	63	3484 (OH), 3083 (CH), 1753 (C=O)	10.74 (s, 1H, COOH), 7.56-7.75 (m, 14H, ArH), 6.80 (s, 1H, CH)
17	H	-C_6H_5	202-205	59	3763 (OH), 1681 (C=O), 1617 (C=N)	12.49 (s, 1H, COOH), 7.43-7.73 (m, 15H, ArH), 6.86 (s, 1H, CH)
18	CH_3	4-Br-C_6H_4	72-275	74	3642 (OH), 3060 (CH, Ar), 1673 (C=O), 1661 (C=N)	12.09 (s, 1H, COOH), 7.22-7.85 (m, 14H, ArH), 2.71 (s, 3H, CH_3)
19	CH_3	4-CH_3-C_6H_4	258-260	71	3867 (OH), 1657 (C=O)	11.99 (s, 1H, COOH), 7.32-7.85 (m, 14H, ArH), 2.95 (s, 3H, CH_3), 1.91 (s, 3H, CH_3)
20	CH_3	3,4-$(OH)_2$- C_6H_4	271-275	48	3577 (OH), 1577 (C=O)	12.39 (s, 1H, COOH), 9.47 (s, 2H, OH), 7.42-7.88 (m, 14H, ArH), 2.47 (s, 3H, CH_3)
21	CH_3	4-NO_2-C_6H_4	284-286	60	3342 (OH) ,1680 (C=O), 1348 (N-O)	12.53 (s, 1H, COOH), 7.32-7.82 (m, 14H, ArH), 2.34 (s, 3H, CH_3)
22	CH_3	4-OH-C_6H_4	246-250	63	3538 (OH), 3078 (CHAr), 1718 (C=O)	12.29 (s, 1H, COOH), 9.40 (s, 1H, OH), 7.50-7.88 (m, 14H, ArH), 2.82 (s, 3H, CH_3)
23	CH_3	4-OCH_3-C_6H_4	288-290	66	3442 (OH), 1680 (C=O), 1225 (C-O)	10.99 (s, 1H, COOH), 7.32-7.82 (m, 14H, ArH), 3.67 (s, 3H, OCH_3), 2.14 (s, 3H, CH_3)
24	CH_3	2-OH-C_6H_4	230-235	73	3546 (OH), 1750 (C=O)	11.39 (s, 1H, COOH), 8.72 (s, 1H, OH), 7.35-7.78 (m, 14H, ArH), 2.25 (s, 3H, CH_3)

Table 3. Mass characterization of test compounds

Comp. **Va**	Mass m/z	Comp. **Vb**	Mass m/z
3	427 (M^+), 411, 335, 279	**3**	411 (M^+), 395, 307, 263
5	448 (M^++2), 447 (M^++1), 446 (M^+), 411	**5**	432 (M^++2), 431 (M^++1), 430 (M^+), 395, 307, 263
8	441 (M^+), 411, 335, 279	**8**	425 (M^+), 395, 307, 263
19	438 (M^+), 425, 363, 305, 279	**19**	423 (M^+), 409, 319, 263
23	454 (M^+), 425, 363, 305, 279	**23**	438 (M^+), 347, 333, 263

Table 4. Anti-anxiety activity of triazine derivatives by forced swimming test.

Compd. **Va**	% immobility (s) ± SEM	Compd. **Va**	% immobility (s) ± SEM	Compd. **Vb**	% immobility (s) ± SEM	Compd. **Vb**	% immobility (s) ± SEM
1	125.47 ± 5.774	**13**	74.23 ± 7.638	**1**	113.27 ± 11.464	**13**	33.08 ± 7.669
2	244.79 ± 5.833	**14**	199.71 ± 3.327	**2**	242.17 ± 14.883	**14**	194.55 ± 7.669
3	246.51 ± 7.609	**15**	240.14 ± 6.831	**3**	243.72 ± 2.94	**15**	236.61 ± 8.585
4	257.86 ± 7.143	**16**	196.03 ± 11.327	**4**	250.74 ± 1.973	**16**	188.28 ± 7.393
5	223.57 ± 4.351	**17**	104.60 ± 2.066	**5**	221.55 ± 3.882	**17**	91.04 ± 10.646
6	239.22 ± 2.475	**18**	235.31 ± 3.0651	**6**	234.82 ± 5.926	**18**	234.46 ± 7.746
7	272.13 ± 5.000	**19**	152.47 ± 8.851	**7**	270.31 ± 6.831	**19**	147.81 ± 6.667
8	247.73 ± 8.516	**20**	253.32 ± 5.164	**8**	245.51 ± 3.667	**20**	241.92 ± 10.138
9	176.58 ± 7.380	**21**	235.31 ± 4.655	**9**	165.93 ± 32.309	**21**	225.49 ± 6.455
10	168.58 ± 3.907	**22**	180.08 ± 10.878	**10**	153.78 ± 6.383	**22**	174.69 ± 28.008
11	17.20 ± 8.975	**23**	32.81 ± 6.952	**11**	156.95 ± 37.025	**23**	28.29 ± 6.952
12	212.51 ± 9.878	**24**	195.43 ± 10.541	**12**	207.99 ± 3.642	**24**	185.66 ± 26.667

Diazepam % immobility (s) ± SEM: 100 ± 3.464

RESULTS

All the synthesized compounds **Va**(**1-24**) and **Vb**(**1-24**) of a series were screened for both anti-anxiety and anti-inflammatory activity.

Anti-anxiety activity

All the compounds **Va** and **Vb** were evaluated by phase I study, a few of these compounds with three different substituents were subjected to phase II study. The reference drug used was diazepam at a dose of 4 mg/kg body weight.

Compound Va derivatives

Compounds **2**, **3**, **4**, **7**, **8** and **20** were found to be the most active with an increase in % immobility (FST model) by 244.79, 246.51, 257.80, 272.13, 247.73 and 253.32, respectively, while other showed moderate activity (Table 4) when compared with the reference drug at the same level of dose of 4 mg/kg. In phase II study (EBT model), % transitions were observed for three compounds, i.e. **1**, **5** and **8**. The results showed that compound **5** had a significant result of 91.70%.

Table 5. Anti-anxiety activity of triazine derivatives by avoidance exploratory behavior test model

Compounds **Va** (**1**, **5**, **8**)	% transitions ± SEM
Diazepam	34.57 ± 25.31
1	78.16 ± 26.200
5	91.70 ± 73.673
8	92.084 ± 52.795

Compound Vb derivatives

Among these compounds, when evaluated by phase-I study, only **4**, **7** and **8** showed good activity with an increase in % immobility by 250.74, 245.51 and 270.31, respectively.

Table 6. Anti-inflammatory activity of triazine derivatives

Comp. **Va**	% inhibition of rat paw edema 1 h	4 h	Comp. **Va**	% inhibition of rat paw edema 1 h	4 h	Comp. **Vb**	% inhibition of rat paw edema 1 h	4 h	Comp. **Vb**	% inhibition of rat paw edema 1 h	4 h
1	88.56 ± 0.052	50.82 ± 0.116	**13**	76.90 ± 0.173	43.68 ± 0.161	**1**	63.83 ± 0.254	42.19 ± 0.163	**13**	68.23 ± 0.116	44.89 ± 0.278
2	86.37 ± 0.047	49.73 ± 0.146	**14**	87.91 ± 0.049	55.77 ± 0.152	**2**	67.38 ± 0.142	47.16 ± 0.038	**14**	72.18 ± 0.391	53.71 ± 0.079
3	93.86 ± 0.042	56.04 ± 0.177	**15**	83.54 ± 0.086	57.47 ± 0.272	**3**	61.54 ± 0.153	38.96 ± 0.059	**15**	69.63 ± 0.059	43.9 9± 0.281
4	84.96 ± 0.057	51.92 ± 0.087	**16**	85.39 ± 0.052	55.49 ± 0.175	**4**	53.87 ± 0.261	27.35 ± 0.139	**16**	63.61 ± 0.163	49.2 6± 0.365
5	79.44 ± 0.180	46.98 ± 0.152	**17**	83.24 ± 0.089	52.19 ± 0.270	**5**	67.32 ± 0.159	45.66 ± 0.251	**17**	64.73 ± 0.253	46.82 ± 0.048
6	77.49 ± 0.173	44.51 ± 0.113	**18**	79.44 ± 0.137	45.33 ± 0.138	**6**	69.59 ± 0.081	51.42 ± 0.084	**18**	59.95 ± 0.279	37.63 ± 0.039
7	86.93 ± 0.047	54.67 ± 0.171	**19**	84.66 ± 0.054	54.395 ± 0.179	**7**	70.62 ± 0.072	56.75 ± 0.329	**19**	66.41 ± 0.152	47.25 ± 0.371
8	89.68 ± 0.048	57.69 ± 0.156	**20**	77.34 ± 0.143	32.42 ± 0.232	**8**	73.94 ± 0.157	59.83 ± 0.271	**20**	67.78 ± 0.261	51.69 ± 0.097
9	96.78 ± 0.019	58.24 ± 0.153	**21**	84.96 ± 0.051	52.19 ± 0.090	**9**	77.27 ± 0.284	61.29 ± 0.189	**21**	62.95 ± 0.019	56.28 ± 0.116
10	56.93 ± 0.101	24.45 ± 0.369	**22**	71.77 ± 0.022	27.47 ± 0.379	**10**	53.71 ± 0.339	21.37 ± 0.386	**22**	54.89 ± 0.062	28.69 ± 0.072
11	85.55 ± 0.06	38.74 ± 0.217	**23**	58.99 ± 0.07	29.67 ± 0.330	**11**	73.11 ± 0.033	57.26 ± 0.096	**23**	47.28 ± 0.269	23.27 ± 0.095
12	65.49 ± 0.138	29.39 ± 0.370	**24**	54.57 ± 0.200	24.45 ± 0.374	**12**	59.39 ± 0.038	24.61 ± 0.379	**24**	42.96 ± 0.371	18.90 ± 0.182

Indomethacin – 79.28% inhibition

Anti-inflammatory activity (Table 6)

All the compounds were evaluated for anti-inflammatory activity by carageenan induced rat paw edema method. The study revealed that among all compounds only **Va** (**3**, **8** and **9**) were found to be the most potential derivatives with % inhibition of 88.23, 84.88 and 91.28, respectively, while the reference drug indomethacin showed 79.28% inhibition.

DISCUSSION AND CONCLUSION

All the triazine derivatives obtained were screened for their anti-anxiety and anti-inflammatory activity. The results indicate that for an anti-anxiety activity the dihydroxy substituent on the phenyl ring at 3, 4 positions yields the compound with better activity than the *para*-, *meta*- and *ortho*-substituted phenyl rings. Also, the dihalogenated phenyl rings showed an increase in % immobility. Besides, the replacement of benzene ring with other heterocyclic moieties resulted in better activity. Further, the compounds bearing sulfur atom showed better activity than the compounds bearing oxygen atom.

Similarly, in case of anti-inflammatory activity, the chalcones of aldehydes gives compounds with better activity as compared to acetophenones and an introduction of allylic group on heterocyclic ring produced good anti-inflammatory activity.

Hence, for anti-anxiety and anti-inflammatory activity, the compounds bearing sulfur atoms showed better activity than those with oxygen atoms. Secondly, compounds with electronegative substituent at the *para* position showed better activity than other substituents. Thus, the new important leads synthesized were evaluated further for their toxicological profile and may serve as a new class of anti-anxiety and anti-inflammatory agents.

REFERENCE:

1. Boerner R.J., Molher M.J.: Pharmacopsychiatry 32,119 (1999).
2. Liebowitz M.R.: J. Clin. Psychiatry 54, 10 (1993).
3. Nishikawa H., Hata T., Itoh E., Funakami Y.: Biol. Pharm. Bull. 27, 352 (2004).

4. Kidwai M., Goel Y., Kumar R.: Indian J. Chem. 37B, 174 (1998).
5. Holla B.S., Gonsalves R., Rao B.S., Shenoy S., Gopalakrishna H.N.: Farmaco 56, 899 (2001).
6. Abdel-Rahman R.M., Morsy J.M., Hanafy F., Amene H.A.: Pharmazie 54, 347 (1999).
7. Partridge M.W., Stevens M.F.G.: J. Chem. Soc. 1127 (1966).
8. Abd E.I., Samii Z.K.: J. Chem. Technol. Biotechnol. 53, 143 (1992).
9. Hay M.P., Prujin F.B., Gamage S.A., Liyanage H.D., Wilson W.R. et al.: J. Med. Chem. 47, 475 (2004).
10. Heilman.W.P., Heilman R.D., Scozzie J.A., Wayner R.J., Gullo J.M, Ariyan Z.S.: J. Med. Chem. 22, 671 (1979).
11. Erickson J.G.: Chem. Heterocycl. Comp. 10, 44 (1956).
12. Jones R.L., Kershaw J.R.: Rev. Pure Appl. Chem. 21, 23 (1971).
13. Porsolt R.D., Bertin A., Jalfre M.: Arch. Int. Pharmacodyn. Ther. 229, 327(1977).
14. Porsolt R.D., Pichon M., Jalfre M.: Nature 266, 730 (1977).
15. Crawley J., Goodwin F.K.: Pharmacol. Biochem. Behav. 13, 167 (1980).
16. Winter C.A., Risley E.A., Nuss G.W.: Proc. Soc. Exp. Biol. Med. 111, 544 (1962).

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