Synthesis and Anti-inflammatory Activity of Some New 1,2,3-Benzotriazine Derivatives Using 2-(4-Oxo-6-phenylbenzo[*d*][1,2,3]triazin-3(4*H*)-yl)acetohydrazide as a Starting Material

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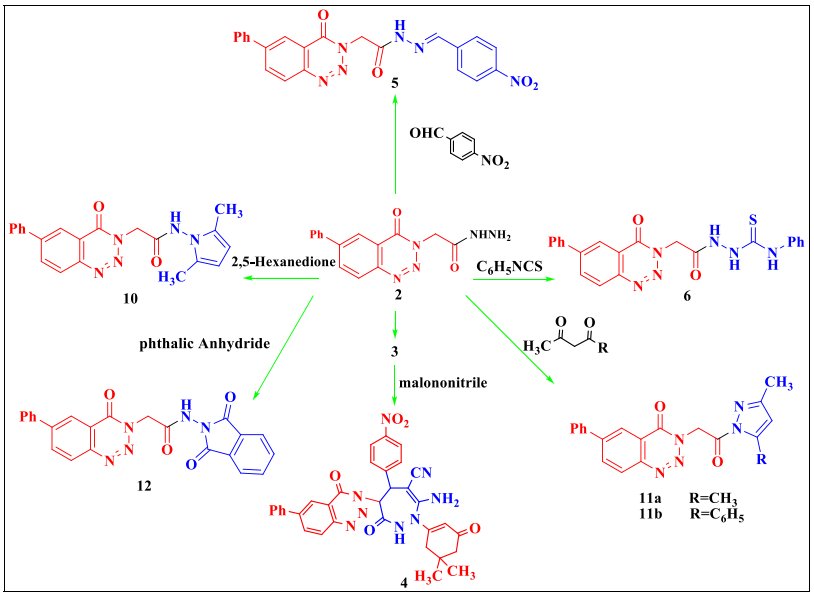

In continuation to our search for new heterocyclic system-based anti-inflammatory activity, a series of novel 1,2,3-benzotriazine derivatives were synthesized. The pharmacological screening showed that many of these compounds have good anti-inflammatory activity. The structure assignments of the new synthesized compounds are based on spectroscopic data, and pharmacological properties are reported.

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INTRODUCTION

Heterocyclic compounds constitute a large group of organic molecules exhibiting a wide range of biological activities that are the basis of life and society. The majority of pharmaceutical products that mimic natural products with biological activity are heterocyclic in nature. 1,2,3-Benzotriazin-4-one is a commonly used motif in a variety of pharmaceutical and agrochemical compounds [1]. For example, azinphos-methyl and azinphos-ethyl are widely used broad-spectrum insecticides and acaricides in crop protection [2]. 1,2,3-Benzotriazine derivatives bearing 2-cyanoiminothia zolidin-4-one moieties had significant inhibitory activities against *Meloidogyne incognita*, which can be utilized as lead compounds [3]. 1,2,3-Triazine represents a widely used lead structure with multitude of interesting applications in the numerous pharmacological fields; thus, various pharmacological activities have been reported and explored till date [4]. In connection with our program work on pyrimidine of expected anti-inflammatory activity, we tried to synthesize new fused substituted benzotriazinones of expected biological activity. Numerous publications have appeared describing the synthesis of 1,2,3-benzotriazines possessing a variety of pharmacological activities, such as anti-inflammatory activity [2–5], cardiovascular activity [6–9], central nervous system activity [10–15], and antimicrobial activities [16]. On the other hand, the prepared 1,2,3-triazine compounds showed antitumor activity, partly by increasing free radicals production and partly by depletion of intracellular catalase, glutathione peroxidase, glutathione reductase, and reduced glutathione. Recently, some new 1,2,3-benzotriazine and their derivatives have been synthesized and used as local anesthetics activity *in vivo* and exhibited a good activity comparable or superior to that of lidocaine [17]. In addition, developed 1,2,3-benzotriazine is linked to beta-lactam as an effective low-molecular-weight synthetic inhibitor of human leukocyte elastase-induced lung damage in

hamsters. In view of this observation and in continuation of our previous work, we synthesized some new 1,2,3-benzotriazine derivatives and tested their anti-inflammatory activity.

RESULTS AND DISCUSSION

Treatment of diazonium salt of methyl-4-aminophenyl-3-carboxylate with ethyl glycinate gave the corresponding benzotriazine derivative **1** (Scheme 1). The IR spectrum of **1** displayed strong absorption bands of two carbonyl of ester and amide at 1739 and 1680 cm^{-1}. The acid hydrazide has been in the center of attention of researchers over many years because of its high reactivity in heterocyclic synthesis as key starting various classes of biologically and pharmacologically active conditions [18]. In addition, substituted hydrazides are characterized by low toxicity [19]. The addition of hydrazine hydrate in the presence of ethanol to compound **1** gave the corresponding acetohydrazide derivative **2** (Scheme 1). The structure of **2** was deduced from their analytical and spectral data where, IR spectrum showed absorption bands ranging from 3311 to 3300 cm^{-1} assignable for NH and NH_2 groups besides two absorption bands for the two carbonyl groups at 1680 and 1662 cm^{-1}. The ^1H NMR spectrum showed NH_2 and NH signals (D_2O exchangeable) at 4.3 and 9.5 ppm. The ^{13}C NMR and mass spectrometry (MS) data of **2** were found to be in full agreement with the proposed structure (cf. Experimental section). The hydrazide derivative **2** prompted us to use it as key starting material for synthesis of some interesting heterocyclic compounds.

When compound **2** was reacted with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) in the presence of toluene, the corresponding triazine-acetohydrazide derivative **3** was formed (Scheme 1). The ^1H NMR showed these singlet signals for the three CH_2 groups at 2.1, 2.2, and 5.1 ppm besides the two methyl groups at 0.97 ppm. The ^{13}C NMR spectrum showed the presence of three carbonyl groups at 155.5, 168.4, and 196.1 ppm. The MS revealed their exact molecule masses (cf. Scheme 1 and Experimental section).

Furthermore, the new diazepinone derivative **4** was prepared via the reaction of enaminone **3** with 2-(4-nitrobenzylidene)malononitrile in ethanol and trimethylamine (Scheme 1). Mechanistically, the reaction is believed to take place via nucleophilic attack of methine group of enaminone **3** on the double bond of malononitrile followed by cyclization (Fig. 1). IR

Scheme 1. Synthetic pathway of diazepinone derivative **4**. [Color figure can be viewed at wileyonlinelibrary.com]

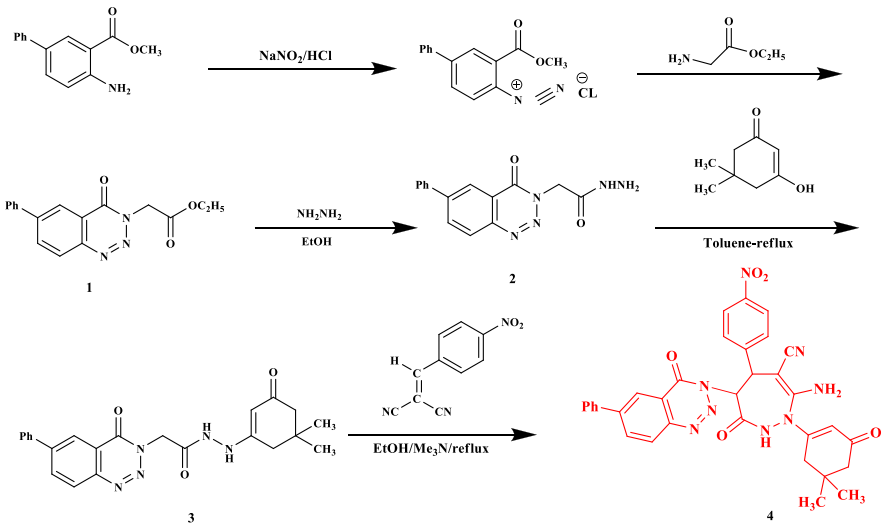


Figure 1. The suggested reaction mechanism for the synthesis of compound **4**.

spectrum showed new absorption bands at 3446–3341 cm^{-1} for NH_2 and NH and at 2184 cm^{-1} for CN. ^1H NMR showed a singlet signal at 0.8 for two methyl groups, two singlet signals at 2.1 and 2.2 for 2 CH_2 of dimedone ring, a singlet signal at 4.45 ppm for CH of dimedone ring, a singlet signal at 6.63 ppm for NH_2, and a singlet signal at 11.2 ppm for NH. Also, the ^1H NMR spectrum showed two CH signals of diazepinone ring at 4.33 (d, J = 1.7, Hz) and 4.93 (d, J = 2.4, Hz) ppm. ^{13}C NMR showed a signal at 117.3 ppm for CN and signals at 157.5, 171.4, and 191.3 ppm for three carbonyl groups. The MS showed the molecular mass m/z = 616, which is in full agreement with the assigned structure.

On treatment of compound **2** with *p*-nitrobenzaldehyde, 4-nitrobenzylidene acetohydrazide derivative **5** was obtained (Scheme 2). The IR spectrum showed the absence of NH_2 group and presence of amidic C═O at 1639 cm^{-1}. ^1H NMR spectrum showed NH signal (D_2O oxide exchangeable) at 12.1 ppm and CH_2 signal at 5.3 ppm. The MS showed exact molecular mass m/z = 428.

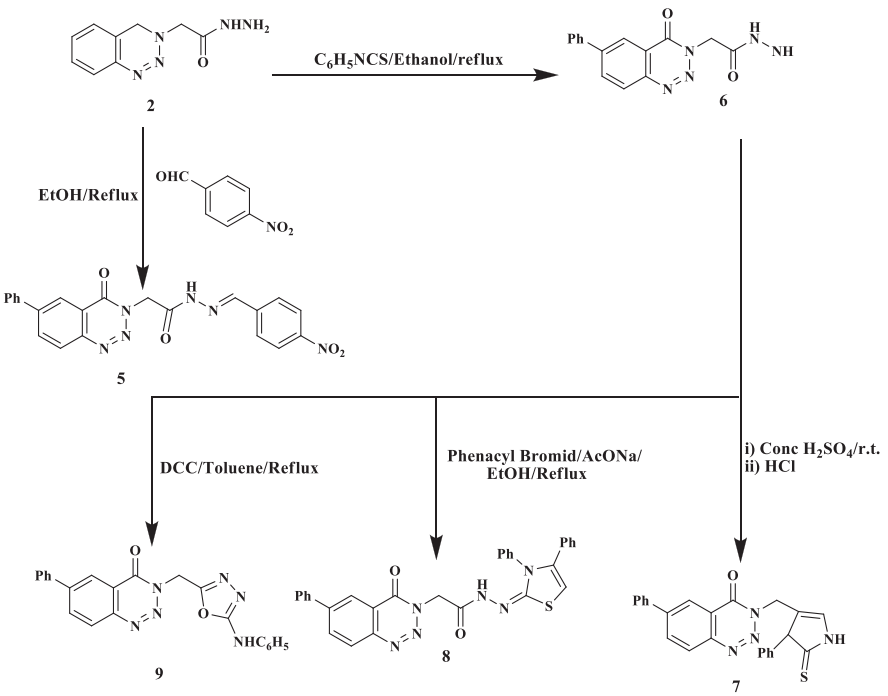
When a mixture of compound **2** refluxed with phenyl isothiocyanate, compound **6** was obtained (Scheme 2). IR spectrum showed absorption bands for 3 (str, NH) and the absence of amino group. The ^1H NMR showed signals for 3 NH at 10 and 10.5 ppm. The MS and NMR are in full agreement with the assigned structure. The cyclization of compound **6** using different media has been discussed. Heating compound **6** with conc. H_2SO_4 gave thioxopyrrole derivative **7** (Scheme 2). IR spectrum showed two absorption bands, one for NH at 3258 cm^{-1} and the other for C═O at 1688 cm^{-1}. The ^1H NMR showed a singlet signal at 5.8 ppm for CH_2, aromatic protons ranging from 6.9 to 8.3 ppm, and a singlet signal at 10 ppm for NH of pyrrole thion ring. The MS showed the molecular mass m/z = 410.

On the other hand, a mixture of compound **6** with phenacylbromide in the presence of fused sodium acetate in alcohol gave 3,4-diphenylthiazole derivative **8** (Scheme 2). IR showed the presence of an absorption band of NH group at 3242 cm^{-1}. The ^1H NMR showed the olefinic hydrogen of thiazole at 4.9 ppm. The ^{13}C NMR and MS showed the expected structure. The mechanism is proposed on the basis of the observed results as shown in Scheme 2; initially, the loss of HBr is followed by intramolecular cyclization to give the expected compound as in Figure 2.

The 1,3,4-oxadiazole derivative **9** was synthesized through one-pot reaction of compound **6** with dicyclohexylcarbodiimide in the presence of toluene (Scheme 2). IR spectrum showed strong absorption bands at 3083 and 1673 cm^{-1} attributed to NH and C═O, respectively. The ^1H NMR spectrum showed a band for NH (exchange with D_2O) at 10.5 ppm. The ^{13}C NMR and MS showed the expected structure.

Treatment of compound **2** with 2,5-hexanedione in acetic acid at room temperature afforded the pyrrole derivative **10** (Scheme 3). The IR spectrum displayed bands for NH and C═O at 3284 and 1681 cm^{-1}, respectively. The ^1H NMR

Scheme 2. Synthesis of novel 1,2,3-benzotriazine derivatives.



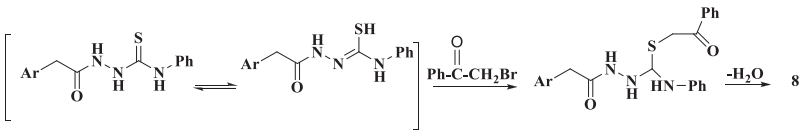
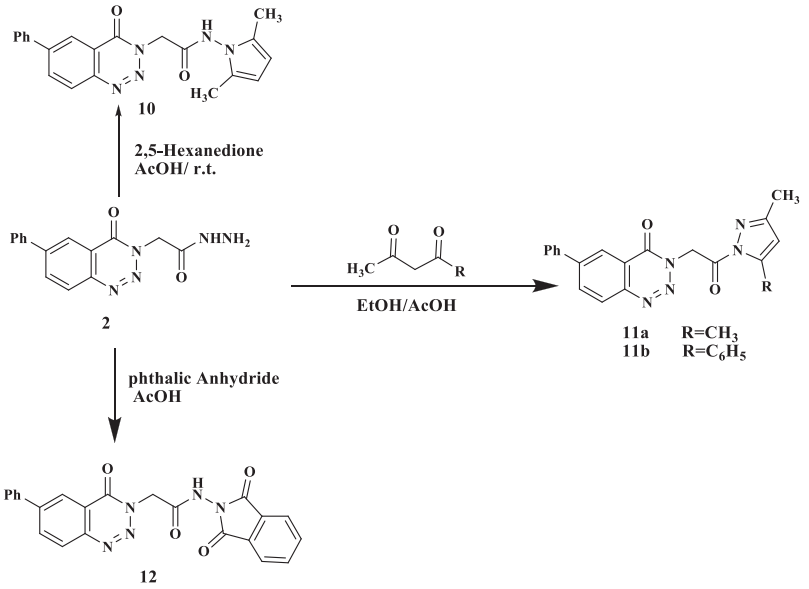


Figure 2. The suggested reaction mechanism for the synthesis of compound **8**.

Scheme 3. Synthesis of pyrrole, pyrazole, and dioxoisoindoline 1,2,3-triazine derivatives.



exhibited signals for NH at 11.14 ppm and doublet of doublet for 2 C═H at 5.6 and 4.9 ppm.

Treatment of **2** with acetyl acetone and benzoyl acetone afforded **11a**, **b** as shown in Scheme 3. Compound **11a** exhibited IR absorption bands at 1680 and 1632 cm^{-1} for amidic C═O. ^1H NMR showed a singlet signal at 5.3 ppm for CH_2, two singlet signals at 2.3 and 2.5 ppm for CH_3, and a singlet signal at 6.3 ppm for ═CH. The ^{13}C NMR and MS showed the expected structure. Also compound **11b** exhibited IR absorption bands at 1690 and 1672 cm^{-1} for amidic C═O. ^1H NMR showed a singlet signal at 2.3 ppm for CH_3, a singlet signal at 5.9 ppm for CH_2, and a singlet signal at 5.6 ppm for ═CH. MS; *m*/*z* = 421.

The reaction of **2** with phthalic anhydride afforded the dioxoisoindolinyl derivative **12** (Scheme 3). The reaction is believed to take place via the initial opening phthalic anhydride and formation of an amide intermediate. The amide intermediate was cyclized by internal nucleophilic attack of nitrogen followed by elimination of water to give the target product **12**, as shown in Figure 3. The IR spectrum showed strong absorption bands at 3197 cm^{-1} for NH and a broad band at 1672–1694 cm^{-1} for four C═O groups. The ^1H NMR spectrum showed a band for CH_2 at 5.3 ppm and at 11.2 ppm for NH. MS; *m*/*z* = 425.

The reaction of 6-phenylbenzo[*d*][1,2,3]triazin-4(3*H*)-one and 2-chloro-*N*-(2-methoxyphenyl)acetamide in dimethylformamide (DMF) afforded compound **13** (Scheme 4). IR showed a band at 3233 cm^{-1} for NH str and two bands at 1687 (C═O) and 1633 (amidic C═O) cm^{-1}. ^1H NMR exhibited a singlet signal at 3.8 ppm for CH_3, a singlet signal at 5.3 ppm for CH_2, and a broad singlet signal at 9.8 ppm for NH. ^{13}C NMR and MS showed the expected structure.

Anti-inflammatory activity assay. Carrageenan-induced rat paw edema model is a suitable test for evaluating anti-inflammatory drugs, which has frequently been used to assess the antiedematous effect of the drug. Carrageenan

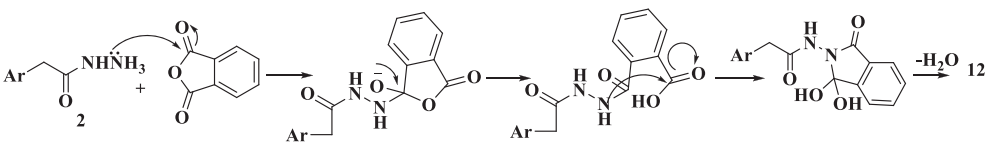
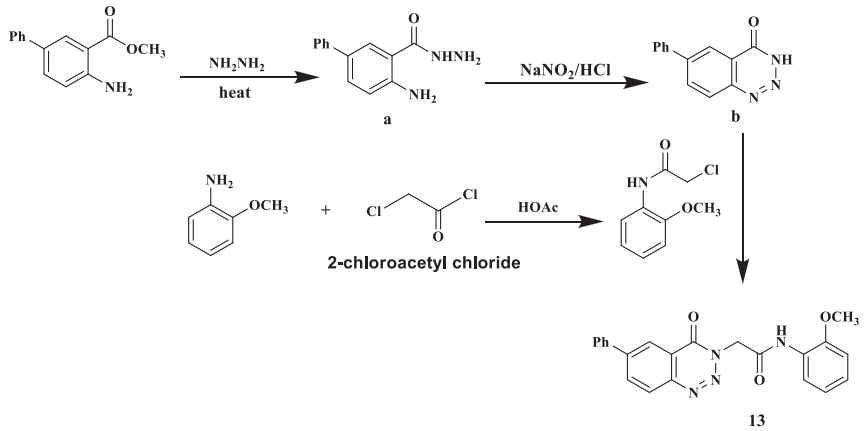


Figure 3. The suggested reaction mechanism for the synthesis of compound **12**.

Scheme 4. Synthesis of [1,2,3]-benzotriazin-3(4*H*)-yl)acetamide **13**.



is a strong chemical used for the release of inflammatory and proinflammatory mediators (prostaglandins and TNF-α, etc.) in carrageen paw edema, for measurement of rat paw volume, and for the calculation of the percentage of rat paw volume that assists in the intensity of the edema. It was obvious from our results that the maximum volume of edema was observed in the control group after 4 h of carrageen injection, which is in accordance with previous literature data; indomethacin, a standard drug at dose of 0.9 mg/100 g and after 4 h of carrageen injection showed anti-inflammatory effect, which is reflected by the inhibition in edema volume. The obtained results of test compounds **11a**, **11b**, and **13** showed strong anti-inflammatory activity, which resemble the result obtained by carrageen; also there were nonsignificant changes between these test compounds and indomethacin. On the other hand, the results obtained from test compounds **4**, **7**, and **9**, compared with control group (indomethacin), showed anti-inflammatory effect, but they were not as significant as those of indomethacin.

EXPERIMENTAL

Melting points were determined using digital Electrothermal 9100 apparatus (Kleinfeld, Gehrden, Germany) and were uncorrected. Fourier transform infrared spectra (KBr) on Varian PerkinElmer 1430 ratio-recording infrared spectrophotometer (Nicolet, Madison, WI, USA). The ^{1}H and ^{13}C NMR spectra (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian Inc., Palo Alto, CA, USA), both using tetramethylsilane as internal standard, and chemical shifts are expressed in δ values. Mass spectrometry was run on a Hewlett-Packard 5988 spectrometer (CSS Analytical Co Inc., Shawnee, KS, USA). Progress of the reaction was monitored by thin-layer chromatography (Merck, Darmstadt, Germany) using sheets precoated with the UV, fluorescent silica gel, 60 F_{254} (Merck), and spots were visualized by iodine vapor or by irradiation with UV light. Elemental analysis was carried out on a PerkinElmer EA1110 CHNS/O analyzer (Life Technologies Ltd., Paisley, UK).

Ethyl 2-(4-oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl) acetate (1). Methyl 4-aminobiphenyl-3-carboxylate (0.039 mol, 6 g) was dissolved in an ice-cooled solution of dilute hydrochloric acid and then diazotized by solution of sodium nitrite (4.25 g) in water (10 mL). A solution of ethyl glycinate hydrochloride (0.039 mol, 5.54 g) was added from a dropping funnel into the stirred solution of the diazonium salt with subsequent neutralization by sodium carbonate. After 1-h stirring, a precipitate was separated and filtered. The solid was washed with water, air-dried, and then crystallized from absolute ethanol as yellow crystals, 9.4 g (68%) of **1**, Rf: 0.59 ($CHCl_3$: MeOH, 1:1); mp 129–131°C [16]; IR: ν_{max}/cm^{-1} 3050 (aromatic CH), 2965 (aliphatic CH), 1739 (ester C═O), 1680 (amidic C═O), 1233 (C–O); MS (EI, 70 eV) *m/z* (%) = 309 (M^+, 12.1%). *Anal*. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.88; H, 4.75; N, 13.29.

2-(4-Oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl) acetohydrazide (2). A mixture of the ester **1** (0.05 mol, 11.65 g) and hydrazine hydrate (98%) (0.05 mol, 2.5 g) in ethanol (20 mL) was stirred for 2 h at room temperature. Excess ethanol was evaporated under vacuum, and the precipitated product was crystallized from ethanol as yellowish white crystals, 10.5 g (77%) of **2**, Rf: 0.41 ($CHCl_3$: MeOH, 1:1); mp 246–248°C; IR: ν_{max}/cm^{-1} 3311–3300 (NH and NH_2), 3070 (aromatic CH), 2957 (aliphatic CH), 1680 (C═O), 1662 (amidic C═O); ^{1}H NMR δ: 4.3 (s, 2H, NH_2), 4.9 (s, 2H, CH_2), 7.9–8.4 (m, 8H, Ar–H), 9.5 ppm (s, 1H, NH, deuterium oxide exchangeable); ^{13}C NMR δ: 54.5 (aliphatic CH_2), 118.7, 121.4, 127.6, 127.9, 128.4, 129.2, 131.4, 138.4, 140.8, 148.4 (Ar–C), 158.4, 170.3 ppm (2 C═O); MS (EI,

70 eV) *m/z* (%) = 295 (M^+, 0.9%), 232 (36.4%), 208 (100%), 77 (80%). *Anal*. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.90; H, 4.22; N, 23.50.

N′-(5,5-Dimethyl-3-oxocyclox-1-enyl)-2-(4-oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl)acetohydrazide (3). A mixture of equimolar amounts of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and hydrazide **2** (0.05 mol) was heated under reflux in toluene (15 mL) for 4 h using Dean–Stark water separator. The reaction mixture was allowed to cool at room temperature. The obtained crystalline product was filtered, dried, and recrystallized from toluene as greenish yellow crystals, 7.5 g (70%) of **3**, Rf: 0.33 ($CHCl_3$: MeOH, 1:1); mp 267–269°C; IR: ν_{max}/cm^{-1} 3197 (2 NH), 2957 (aliphatic CH), 1710 (br, 2 C═O), 1690 (amidic C═O), 1583 (NH bending scissoring); ^{1}H NMR δ: 0.97 (s, 3 H, CH_3), 1.02 (s, 3H, CH_3), 2.1 (s, 2H, CH_2), 2.2 (s, 2H, CH_2), 5.1 (s, 1H, ═CH), 5.2 (s, 2H, N–CH_2), 8.8 (s, 1H, ═C–NH), 7.9–8.3 (m, 8H, Ar–H), 10.3 ppm (s, 1H, NH–CO); ^{13}C NMR δ: 27.5 (2 CH_3), 40.3, 49.5, 55.32, 101, 163 (3 CH_2, *C*Me_2, 2 ═C), 116.6, 121.9, 127.3, 127.6, 128.7, 129.2, 131.6, 138.4, 140.9, 148.6 (Ar–C), 155.5, 168.4, and 196.1 ppm (3 C═O); MS (EI, 70 eV) *m/z* (%) = 417 (2.1%), 416 (3%), 331 (4.1%), 203 (88.8%), 77 (100%). *Anal*. Calcd. for $C_{23}H_{23}N_5O_3$: C, 66.17; H, 5.55; N, 16.78. Found: C, 66.05; H, 5.42; N, 16.59.

3-Amino-2-(5,5-dimethyl-3-oxocyclohex-1-enyl)-5-(4-nitrophenyl)-7-oxo-6-(4-oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl)-2,5,6,7-tetrahydro-1H-1,2-diazepine-4-carbonitrile (4). A mixture of equimolar amounts of enaminone **3** and 2-(4-nitrobenzylidene)malononitrile (0.001 mol) in ethanol (15 mL) containing four drops of trimethylamine was heated under reflux for 12 h. The reaction mixture was cooled, and the precipitated product was filtered, washed with water, and crystallized from ethanol as yellow crystals, 5.5 g (44%) of **4**, Rf: 0.37 ($CHCl_3$: MeOH, 1:1); mp 298–299°C; IR: ν_{max}/cm^{-1} 3446 (NH_2), 3341 (NH), 3020 (aromatic CH), 2958 (aliphatic CH), 2184 (CN), 1690 (br, 2 C═O), 1680 (amidic C═O), 1650 (conj, C═C); ^{1}H NMR δ: 0.8 (s, 6H, CH_3), 2.1 (s, 2H, dimedone CH_2), 2.2 (s, 2H, dimedone CH_2), 4.45 (s, 1H, dimedone CH), 4.93 (d, *J* = 2.4, Hz, 1H, diazepinone CH), 4.33 (d, *J* = 1.7, Hz, 1H, diazepinone CH), 6.63 (s, 2H, NH_2), 7.5–8.3 (m, 12H, Ar–H), 11.2 ppm (s, 1H, NH, deuterium oxide exchangeable); ^{13}C NMR δ: 27.7 (2 CH_3), 28.5 (diazepinone CH_2), 31.9 (CMe_2), 36.5 (dimedone CH_2), 52.5 (dimedone CH_2), 63.2 (diazepinone CH), 68.3 (diazepinone CH_2), 100.1 (dimedone CH), 117.3 (CN), 119.6, 121.4, 125.3, 127.6, 127.7, 127.9, 128.6, 128.9, 129.2, 131.4, 138.6, 140.8, 144.1, and 148.5 (Ar–C), 155.1 (dimedone C), 157.5, 171.4, 191.3 (3 C═O), 160.5 ppm (diazepinone $CHNH_2$); MS (EI, 70 eV) *m/z* (%) = 616 (M^+, 10.2%). *Anal*. Calcd. for $C_{33}H_{28}N_8O_5$: C, 64, 28; H, 4.58; N, 18, 17. Found: C, 64, 12; H, 4.37; N, 18, 09.

(E)-N′-(4-Nitrobenzylidene)-2-(4-oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl)acetohydrazide (5). To a solution of the hydrazide **2** (0.002 mol, 0.438 g) in absolute ethanol (10 mL), *p*-nitrobenzaldehyde (0.002 mol) was added. The reaction mixture was refluxed for 3 h, and the precipitated product was filtered, washed with water, and crystallized from ethanol as deep yellow crystals, 0.29 g (55%) of **5**, Rf: 0.32 ($CHCl_3$: MeOH, 1:1); mp 292–294°C; IR: ν_{max}/cm^{-1} 3388–3216 (NH), 3072 (aromatic CH), 2958 (aliphatic CH), 1670 (C═O), 1639 (amidic C═O), 1614 (C═N); ^{1}H NMR δ: 5.3 (s, 2H, CH_2), 5.7 (s, 1H, ═CH), 7.9–8.3 (m, 12H, Ar–H), 12.1 ppm (s, 1H, NH); ^{13}C NMR δ: 119.2, 124.0, 124.4, 125.3, 127.6, 127.8, 127.9, 128.1, 128.7, 129.1, 131.1, 138.6, 140.8, 144.1, 148.4, 151.2 (Ar–C), 146.2 (C═N), 159.5, 171.3 ppm (2 C═O); MS (EI, 70 eV) *m/z* (%) = 428 (M^+, 3.2%). *Anal*. Calcd. for $C_{22}H_{16}N_6O_4$: C, 61.68; H, 3.76; N, 19.62. Found: C, 61.55; H, 3.62; N, 19.50.

2-(2-(4-Oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl)aceto phenylhydrazine carbothioamide (6). A mixture of compound **2** (0.012 mol, 2.634 g) and phenyl isothiocyanate (0.012 mol, 1.62 g) in ethanol (15 mL) was refluxed for 1 h, and the precipitated product was filtered and crystallized from ethanol as yellow crystals, 3.29 g (76%) of **5**, Rf: 0.27 ($CHCl_3$: MeOH, 1:1); mp 261–262°C; IR: ν_{max}/cm^{-1} 3050 (aromatic CH), 3331, 3227, 3219 (3 NH), 2931 (aliphatic CH), 1688 (C═O), 1630 (amidic C═O), 1300 (C═S); ^{1}H NMR δ: 5.2 (s, 2H, CH_2), 7.2–8.3 (m, 13H, Ar–H), 10 (s, 2H, 2NH), 10.5 ppm (s, 1H, NH). ^{13}C NMR δ: 55.1 (aliphatic CH_2), 119.6, 124.3, 124.4, 125.1, 127.6, 127.8, 127.9, 128.5, 128.9, 129.3, 131.4, 138.4, 138.6, 140.5, 148.4, 151.2 (Ar–C), 159.5, 170.3 (2 C═O), 186.2 ppm (C═S). MS (EI, 70 eV) *m/z* (%) = 430 (M^+, 9.1%). *Anal*. Calcd. for $C_{22}H_{18}N_6O_2S$: C, 61.38; H, 4.21; N, 19.72. Found: C, 61.15; H, 4.02; N, 19.58.

6-Phenyl-3-((4-phenyl-5-thioxo-4,5-dihydro-1H-pyrrol-3-yl)methyl)benzo[d][1,2,3]triazin-4(3H)-one (7). The thiosemicarbazide **6** (0.001 mol, 0.354 g) was dissolved in concentrated sulfuric acid (5 mL) while being cooled and was allowed to stand for 15 min. The reaction mixture was then quenched with ice and treated with concentrated ammonia solution till neutral to litmus paper. The precipitate product was crystallized from ethanol as yellow crystals, 0.29 g (76%) of **7**, Rf: 0.41 ($CHCl_3$: MeOH, 1:1); mp 271–273°C; IR: ν_{max}/cm^{-1} 3258 (NH), 2937 (aliphatic CH), 3051 (aromatic CH), 1688 (C═O); ^{1}H NMR δ: 3.88 (s, 2H, aliphatic CH_2), 5.8 (s, 1H, pyrrole thion ═CH,), 6.9–8.3 (m, 14H, Ar–H and olefinic CH═C), 10 ppm (s, NH); ^{13}C NMR δ: 57.2 (aliphatic CH_2), 63.5 (pyrrole thion CH), 115.7 (pyrrole thion ═C), 118.1, 123.3, 124.5, 125.1, 127.3, 127.6, 127.9,

128.3, 128.7, 129.1, 131.3, 138.4, 140.1, 142.8, 144.1, 148.4, 151.2 (Ar–C), 128.5 (pyrrole thion =CH), 171.3 (C=O), 192.2 ppm (C=S); MS (EI, 70 eV) *m/z* (%) = 410 (M^+, 3.1%). *Anal*. Calcd. for $C_{24}H_{18}N_4OS$: C, 70.22; H, 4.42; N, 13.65. Found: C, 70.05; H, 4.21; N, 13.44.

(E)-N-(3,4-Diphenylthiazol-2(3H)-ylidene)-2-(4-oxo-6-phenylbenzo[d][1,2,3]triazin-3(4H)-yl)acetohydrazide (8). A mixture of **6** (0.001 mol, 0.354 g), phenacylbromide (0.001 mol, 0.233 g), and fused sodium acetate (0.328 g, 0.004 mol) was heated in absolute ethanol (10 mL) under reflux for 10 h while being stirred. The mixture was cooled and diluted with water, and the separated product was crystallized from ethanol as yellowish green crystals, 0.59 g (72%) of **8**, Rf: 0.53 ($CHCl_3$: MeOH, 1:1); mp 283–285°C; IR: ν_{max}/cm^{-1} 3242 (NH), 3050 (aromatic CH), 2951 (aliphatic CH), 1680 (C=O), 1623 (amidic C=O); ^{1}H NMR δ: 4.9 (s, 1H, =CH), 5.6 (s, 2H, CH_2), 7.5–8.2 (m, 18H, Ar–H), 10.5 ppm (s, 1H, NH); ^{13}C NMR δ: 54.5 (aliphatic CH_2), 106.3, 147.7, 149.13 (thiazole C), 119.8, 121.2, 124.2, 127.6, 127.9, 128.2, 128.8, 129.5, 130.4, 131.4, 138.5, 140.6, 141.5, 141.9 (Ar–C), 158.5, 172.4 ppm (2 C=O); MS (EI, 70 eV) *m/z* (%) = 530 (M^+, 2.4%). *Anal*. Calcd. for $C_{30}H_{22}N_6O_2S$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.77; H, 4.14; N, 15.69.

6-Phenyl-3-(5-(phenylamino)-1,3,4-oxadiazol-2yl) methylbenzo[d][1,2,3]triazin-4(3H)-one (9). A mixture of **6** (0.001 mol, 0.354 g) and dicyclohexylcarbodiimide (0.001 mol, 0.2 g) in toluene (10 mL) was refluxed for 12 h. The reaction mixture was cooled, and the separated solid was filtered. The clear filtrate was concentrated, and the separated product was filtered off and crystallized from ethanol as faint yellow crystals, 0.32 g (62%) of **9**, Rf: 0.47 ($CHCl_3$: MeOH, 1:1); mp 295–297°C; IR: ν_{max}/cm^{-1} 3313 (NH), 3083 (aromatic CH), 2948 (aliphatic CH_2), 1673 (C=O); ^{1}H NMR δ: 5.8 (s, 2H, CH_2), 6.9–8.3 (m, 13H, Ar–H), 10.5 ppm (s, 1H, NH); ^{13}C NMR δ: 49.5 (CH_2), 117.8, 118.6, 122.4, 124.1, 127.1, 127.9, 128.4, 129.2, 131.7, 138.5, 139.9, 140.3, 148.4 (Ar–C), 157.6 (C=O), 162.9, 169.3 ppm (oxadiazole C); MS (EI, 70 eV) *m/z* (%) = 396 (M^+, 3.2%). *Anal*. Calcd. for $C_{22}H_{16}N_6O_2$: C, 66.66; H, 4.07; N, 21.20. Found: C, 66.51; H, 3.97; N, 21.11.

N-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-(4-oxo-6-phenylbenzo [d][1,2,3]triazin-3(4H)-yl)acetamide (10). A mixture of hydrazide **2** (0.002 mol, 0.438 g) and 2,5-hexanedione (0.002 mol, 0.25 mL) in glacial acetic acid (5 mL) was stirred at room temperature overnight. On diluting the mixture with water, the precipitate product was filtered off and crystallized from ethanol as yellowish white crystals, 0.49 g (72%) of **10**, Rf: 0.53 ($CHCl_3$: MeOH, 1:1); mp 269–270°C; IR: ν_{max}/cm^{-1} 3284 (NH), 3067 (aromatic CH), 2978 (aliphatic CH_2), 1681 (C=O), 1620 (amidic C=O); ^{1}H NMR δ: 2.1 (s, 6H, $2CH_3$), 5.3 (s, 2H, CH_2), 5.6 and 5.9 (dd, *J* = 1.7, 4.8 Hz, 2H, 2 =CH), 7.9–8.3 (m, 8H, Ar–H), 11.14 ppm (s, 1H, NH); ^{13}C NMR δ: 19.1 (2 CH_3), 56.9 (aliphatic CH_2), 105.5, 106.8, 116.3, 126.2 (pyrrole C), 119.9, 121.2, 127.6, 127.9, 128.8, 129.6, 131.4, 138.9, 140.5, 148.3, 158.4, 171.2 (Ar–C), 158.4, 171.2 ppm (2 C=O); MS (EI, 70 eV) *m/z* = 373 (M^+, 2.3%). *Anal*. Calcd. for $C_{21}H_{19}N_5O_2$: C, 67.55; H, 5.13; N, 18.76. Found: C, 67.33; H, 4.95; N, 18.59.

General procedures of compounds (11a, b). A solution of hydrazide **2** (0.002 mol, 0.438 g) was treated with the respective active methylene compounds (acetyl acetone and benzoyl acetone) (0.002 mol) in ethanol (10 mL). The mixture was refluxed for 6 h and then poured into water to give a precipitate. The precipitate was collected, washed with water several times, and recrystallized from ethanol to afford **11a**, **b**.

3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-6-phenylbenzo[d][1,2,3]triazin-4(3H)-one (11a). Yellow crystals, 0.29 g (72%) of **11a**, Rf: 0.48 ($CHCl_3$: MeOH, 1:1); mp 280–282°C; IR: ν_{max}/cm^{-1} 3080 (aromatic CH), 2991 (aliphatic CH), 1680 (C=O), 1632 (amidic C=O); ^{1}H NMR δ: 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 5.3 (s, 2H, CH_2), 6.3 (s, 1H, =CH), 7.4–8.5 ppm (m, 8H, Ar–H); ^{13}C NMR δ: 13.3, 13.62 (2 CH_3), 49.9 (aliphatic CH), 110.2 (pyrazole CH), 120.2, 122.3, 127.7, 127.9, 128.3, 123.6, 130.7, 137.8, 141.2, 148.3, 159.4, 170.3 (Ar–C), 143.8, 153.3 (pyrazole C), 159.5, 170.1 ppm (2 C=O); MS (EI, 70 eV) *m/z* (%) = 359 (M^+, 11.1%). *Anal*. Calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.77; H, 4.72; N, 19.33.

3-(2-(3-Methyl-5-phenyl-1H-pyrazol-1-yl)-2-oxoethyl)-6-phenylbenzo[d][1,2,3]triazin-4(3H)-on (11b). Yellowish white crystals, 0.25 g (65%) of **11b**, Rf: 0.43 ($CHCl_3$: MeOH, 1:1); mp 289–292°C; IR: ν_{max}/cm^{-1} 3086 (aromatic CH), 2998 (aliphatic CH), 1690 (C=O), 1672 (amidic C=O); ^{1}H NMR δ: 2.3 (s, 3H, CH_3), 5.6 (s, 1H, =CH), 5.9 (s, 2H, CH_2), 7.3–8.3 ppm (m, 13H, Ar–H); ^{13}C NMR δ: 13.3 (CH_3), 55.4 (aliphatic CH_2), 106.3 (pyrazole CH), 118.1, 123.2, 124.1, 125.3, 127.3, 127.5, 127.9, 128.5, 128.3, 129.3, 131.1, 138.4, 138.7, 140.5, 148.4, 151.2 (Ar–C), 133.6, 146.3 (pyrazole C), 160.5, 172.3 ppm (2 C=O); MS (EI, 70 eV) *m/z* (%) = 421 (M^+, 12.3%). *Anal*. Calcd. for $C_{25}H_{19}N_5O_2$: C, 71.25; H, 4.54; N, 16.62. Found: C, 71.09; H, 4.38; N, 16.53.

N-(1,3-Dioxoisoindolin-2-yl)-2-(4-oxo-6-phenylbenzo[d] [1,2,3]triazin-3(4H)-yl)acetamide (12). A mixture of hydrazide **2** (0.002 mol, 0.438 g), phthalic anhydride (0.002 mol, 0.296 g) in absolute ethanol (10 mL) with a few drops of glacial acetic acid was refluxed for 6 h. The reaction mixture was concentrated to obtain compound **12**, which was crystallized from ethanol as yellowish white crystals, 0.51 g (78%) of **12**, Rf: 0.33 ($CHCl_3$: MeOH, 1:1); mp 282–284°C; IR: ν_{max}/cm^{-1} 3197 (NH), 3093 (aromatic CH), 2991 (aliphatic CH), broad band 1672–1694 (4 C=O); ^{1}H NMR δ: 5.3 (s, 2H,

Table 1

The anti-inflammatory activity of the new compounds (mean + SE).

Groups	Initial thickness (zero time)	Thickness of rat paw (mm) after			
		1 h	2 h	3 h	4 h
Control	2.0 ± 0.0	5.75 ± 0.25	6.75 ± 0.25	7.37 ± 0.24	7.37 ± 0.24
Indomethacin	2.1 ± 0.22	2.12 ± 0.12[a]	2.25 ± 0.25[a]	3.25 ± 0.25[a]	3.75 ± 0.14[a]
Celecoxib	2.0 ± 0.0	3.22 ± 0.25[a,b]	3.75 ± 0.31[a,b]	3.75 ± 0.25[a] NS	3.87 ± 0.31[a] NS
4	2.1 ± 0.25	4.0 ± 0.2[a,b]	4.75 ± 0.14[a,b]	5.0 ± 2.0[a,b]	5.12 ± 0.125[a,b]
7	2.0 ± 0.0	3.75 ± 0.25[a,b]	4.2 ± 0.12[a,b]	4.62 ± 0.24[a,b]	5.25 ± 0.14[a,b]
9	2.0 ± 0.0	3.75 ± 0.25[a,b]	4.75 ± 0.14[a,b]	4.75 ± 014[a,c]	4.25 ± 0.14[a,d]
11a	2.0 ± 0.0	2.12 ± 0.125[a] NS	2.75 ± 0.14[a] NS	3.5 ± 0.2[a] NS	3.75 ± 0.32[a] NS
11b	2.1 ± 0.2	3.25 ± 0.25[a,b]	4.37 ± 0.24[a,b]	4.5 ± 0.24[a,b]	3.75 ± 0.32[a] NS
13	2.0 ± 0.0	2.75 ± 0.14[a,c]	3.12 ± 0.125[a,c]	3.25 ± 0.25[a] NS	3.25 ± 0.14[a] NS

NS, nonsignificant.
[a]Compared with control (carrageenan only), $p < 0.001$.
[b]Compared with indomethacin, $p < 0.001$.
[c]Compared with indomethacin, $p < 0.01$.
[d]Compared with indomethacin, $p < 0.05$.

CH_2), 7.9–8.3 (m, 12H, Ar–H), 11.2 ppm (s, 1H, NH); ^{13}C NMR δ: 56.6 (aliphatic CH_2), 121.6, 124.3, 123.4, 124.1, 127.3, 127.8, 127.9, 128.6, 128.9, 129.2, 131.4, 138.4, 138.6, 140.5, 149.4, 151.2 (Ar–C), 160.5, 166.2, 168.3, 171.3 ppm (4 C═O); MS (EI, 70 eV) *m/z* (%) = 425 (M^+, 15.2%). *Anal.* Calcd. for $C_{23}H_{15}N_5O_4$: C, 64.94; H, 3.55; N, 16.46. Found: C, 64.78; H, 3.42; N, 16.20.

N-(2-Methoxyphenyl)-2-(4-oxo-6-phenylbenzo[d][1,2,3] triazin-3(4H)-yl)acetamide (13). A mixture of 6-phenylbenzo[*d*][1,2,3]triazin-4(3*H*)-one (0.002 mol, 0.294 g) and 2-chloro-*N*-(2-methoxyphenyl)acetamide (0.002 mol) was refluxed for 4 h in DMF in the presence of anhydrous potassium carbonate. The mixture was cooled, diluted with water, and then filtered. The separated solid was washed with ethanol, dried, and crystallized from DMF/ethanol mixture as reddish yellow crystals, 0.21 g (65%) of **13**, Rf: 0.53 ($CHCl_3$: MeOH, 1:1); mp 273–275°C; IR: ν_{max}/cm^{-1} 3233 (NH), 3023 (aromatic CH), 2976 (aliphatic CH), 1687 (C═O), 1633 (amidic C═O); ^1H NMR δ: 3.8 (s, 3H, CH_3), 5.3 (s, 2H, CH_2), 6.9–8.3 (s, 12H, Ar–H), 9.8 amidic (br, 1H, NH); ^{13}C NMR δ: 53.1 (aliphatic CH_2), 55.2, (OCH_3), 113.5, 114.5, 119.6, 119.9, 121.2, 121.8, 127.6, 127.8, 129.7, 130.8, 131.4, 138.5, 148.3 (Ar–C), 158.4, 170.2 ppm (2 C═O); MS (EI, 70 eV) *m/z* (%) = 386 (M^+, 9.1%). *Anal.* Calcd. for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.22; H, 4.53; N, 14.32.

Anti-inflammatory activity evaluation. The rat hind paw edema method [20] was applied to determine the anti-inflammatory activity of the test compounds (**4**, **7**, **9**, **11a**, **11b**, and **13**) using indomethacin as a standard. Mature albino rats of both sexes weighing 150–200 g were used. They were divided into 10 equal groups (each with five). The first group was left as a control, while the second group was injected [intraperitoneally (IP)] with indomethacin at a dose of 0.9 mg/100 g. The test compounds were injected (IP) to six groups at the same dose level, whereas the last group was injected (IP) with celecoxib at the dose of 0.9 mg/100 g. One hour later, edema in the right hind paw was induced by injection of 0.1 mL of 10% carrageen. The thickness of the paw was measured 1, 2, 3, and 4 h after carrageen injection to determine the anti-inflammatory activity of the test compounds (Table 1).

CONCLUSION

A series of new heterocyclic compounds of some 1,2,3-benzotriazine derivatives were synthesized in this study with the hope of discovering a new structure that leads to serving as potent anti-inflammatory agents. On the basis of these screening results, compounds **11a**, **11b**, and **13** showed significant activity in induced carrageen paw edema and have been targeted for further studies, with nonsignificant changes between these test compounds and standard drug (indomethacin). New compounds were elucidated by chemical and spectroscopic data.

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