Synthesis of Tetrazoloquinoline-Based Mono- and Bisphosphonate Esters as Potent Anti-Inflammatory Agents

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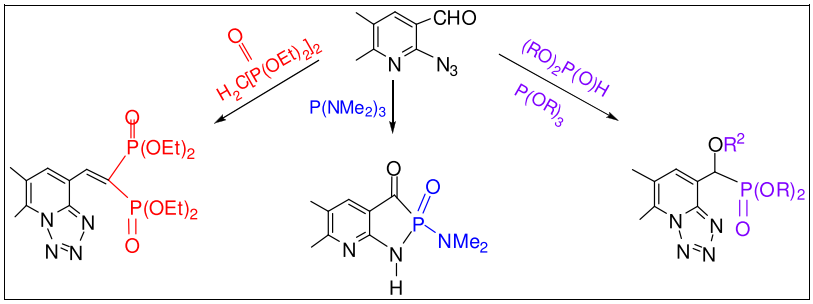

Several new α-alkoxy- and α-hydroxyphosphonate derivatives of tetrazole-quinolines were synthesized from the reaction of 2-azidoquinolines 3-carboxaldehyde **1a,b** with trialkyl phosphites and dialkyl phosphites. On the other hand, azaphospholes **12a,b** were obtained by treating **1a,b** with tris(dimethylamino) phosphine. Furthermore, Perkin-type condensation of **1a,b** and tetraethyl methylenebisphosphonate provided the corresponding tetrazoloquinoline-based bisphosphonate esters **14a,b**. Based on the prediction results (PASS program), the anti-inflammatory activity of the prepared compounds was determined *in vivo* by the acute carrageenin-induced paw edema in rats. Many of the new compounds exhibit considerable anti-inflammatory properties at a dose of 50 mg/kg body weight. Especially **14a** and **14b** revealed remarkable activities compared with indomethacin, which was used as a reference standard in this study.

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INTRODUCTION

The presence of quinolines in an abundant number of natural products and pharmaceutically active compounds continues to fuel the desire to develop new and/or improved methods for their synthesis [1–4]. Many representatives have found clinical uses for the treatment of tumor diseases [5,6]. There have also been reviews on quinoline derivatives and their antibiotic properties in multidrug resistant *Enterbacter aerogenes* isolates [7]. Relatively few reports about synthesis and bioactivity of quinolines incorporating a mono- or a bisphosphonate moiety are reported in the literature [8–10].

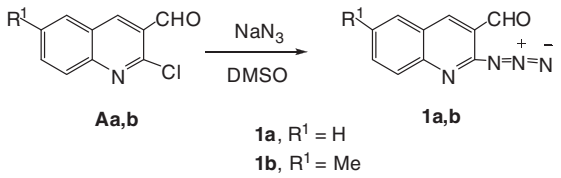
As part of our program on the application of phosphorus compounds in pharmaceutical synthesis, we have been involved over the last two decades or so in the invention and development of phosphono substituted N-heterocycles prepared *via* application of phosphorus reagents to C═N multiple bonds [11–17]. Biological activity studies of selected products have been investigated, and the results showed that some of new phosphonates and specially the diphosphonates have recognized responses to the chronic inflammatory associated with cutaneous granuloma formation and erosive arthritis [11,12].

In this account, we describe our study on the synthesis of phosphono substituted quinolines containing a highly bioactive tetrazole moiety [18–20] as a development of our research work. The approach is achieved by reacting 2-azido-3-carbaldehyde-quinolines **1a** and **1b** with trialkyl phosphites **3a–3c**, dialkyl phosphites **7a–7c**, tris(dimethylamino)phosphine **8**, and Horner–Emmons reagent **13**. The study focused on the preferable attack of the phosphorus reagents at the carbonyl or the azide group in the bifunctional substrates **1a** and **1b**. Furthermore, the prospective potency of our products for treating the inflammatory disease was based on the results of the prediction that had been carried out, in the earlier stage. The computer-assisted molecular modeling (CAMM), prediction of activity spectra for substances (PASS) program, was adopted for designing—*in silico*—the structures of potentially active molecules for future synthesis. Later on, the *in vivo* activity of the synthesized phosphonates and bisphosphonates in the rat adjuvant model was also studied in terms of structure–activity relationships.

RESULTS AND DISCUSSION

The reaction procedure for the preparation of the titled compounds, tetrazoloquinoline-based mono- and diphosphonate esters, and the course of the reactions were depicted in Schemes 1–6. The required starting materials 2-(λ^5-triaz-1-en-2yl)quinoline-3-carbaldehyde (known as 2-azidoquinoline-3-carbaldehyde **1a**) and the new

Scheme 1

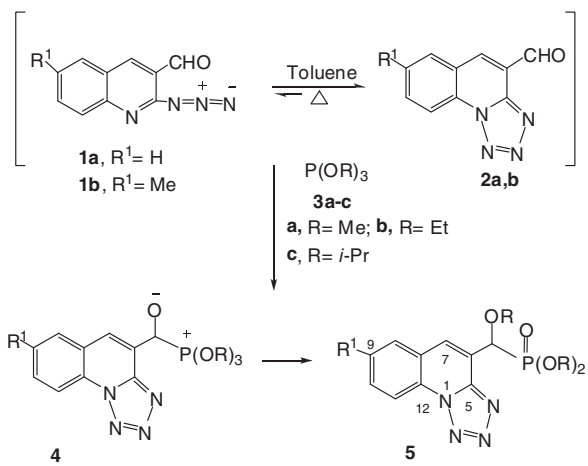


6-methyl-2-(λ^5-triaz-1-en-2-yl)-quinoline-3-carbaldehyde (known as 2-azido-6-methylquinoline-3-carbaldehyde, **1b**) were prepared according to the literature with little modification in ~80% yield by treating the parent chloride **Aa** or **Ab** with sodium azide in dimethylsulfoxide (DMSO; Scheme 1) [21,22].

Treatment the azide **1a** with trimethyl **3a** or triethyl phosphite **3b** in toluene solution, and heating the reaction mixture under reflux for ~4 h led to the formation of dialkyl alkoxy (tetrazolo[1,5-a]-quinolin-6-yl)methylphosphonates **5a,b** in ≥80% yield. A plausible mechanism for the formation of tetrazolophosphonates **5a,b** is displayed in Scheme 2. On heating, the equilibrium between tetrazole **2** and its isomeric 2-azidoquinoline **1** presents exclusively at the tetrazole **2**. The last observation is consistent with the earlier characterization data reported for the azide **1** [21,22]. Compound **2** is then intercepted by the nucleophilic attack of the phosphite-phosphorus on the carbonyl-carbon in **2** to give the dipolar species **4**, which is followed by intramolecular group translocation to yield **5a** or **5b**.

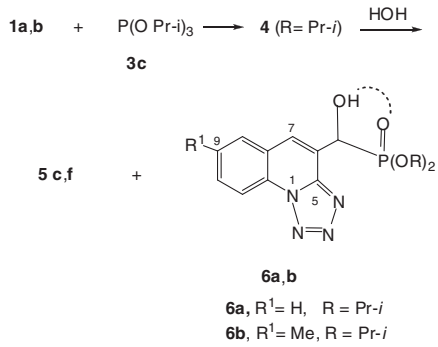
The composition of the structure **5** was based on the recorded elemental analyses, molecular weight determinations mass spectroscopy (MS), and spectroscopic data. Compounds **5a,b** showed the ^{31}P-NMR chemical shifts

Scheme 2



Cpd.	R^1	R	Cpd	R^1	R
5a	H	Me	**5d**	Me	Me
5b	H	Et	**5e**	Me	Et
5c	H	*i*-Pr	**5f**	Me	*i*-Pr

Scheme 3

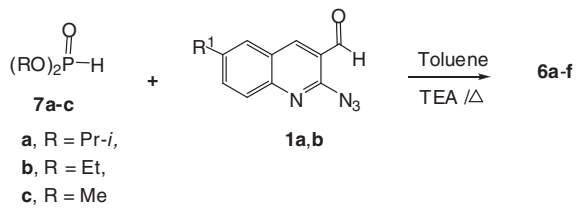


around δ 27 ppm. Their IR spectra revealed the absence of stretching vibration bands at 1710 and 2100 cm^{-1} regions, related to the carbonyl and the azido group of the azides **1a,b**. Instead, they showed strong bands at 1185 cm^{-1} assigned to the tetrazole stretching and at 1036, 1256 cm^{-1} that assigned to P—O—C and P=O vibrations. In the ^{1}H-NMR spectrum of compound **5a**, the exocyclic methine proton (aldehydic) present in the spectrum of **1a** at δ 10.35 ppm, was displayed at δ 5.75 (d, $^2J_{P-H}$ = 18.8 Hz) ppm; the deshielding of the methane proton signal is clearly due to the phosphorus entity. ^{13}C-NMR data also confirmed the assigned structure.

In a similar way, the reaction products of **1b** with trimethyl and triethyl phosphites were assigned the analogous structures **5d** (84%) and **5e** (87%). Nevertheless, treatment of **1a,b** with triisopropyl phosphite **3c** afforded a mixture of the expected analogues **5c,f** (~47%) together with α-hydroxyphosphonates **6a,b** (~10%, Scheme 3). This behavior is not unexpected as the bulky isopropyl group would impede the alkyl migration in the second step, allowing a partial hydrolysis with fortuitous moisture at the stage of the dipolar intermediate **4** to give the side-products **6a,b**, along with **5c,f**. It is known that lengthening the alkyl radicals in trialkyl phosphites results in reduction of their migration aptitude [23].

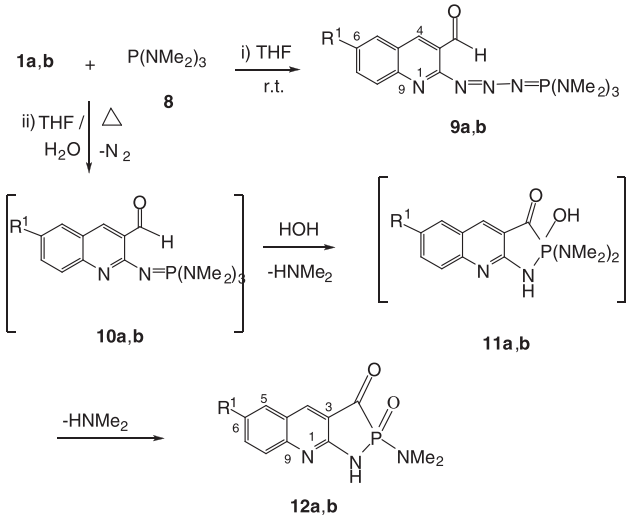
Furthermore, compounds **6a,b** were unequivocally obtained in (~90% yield) when **1a,b** were allowed to react

Scheme 4



Cpd.	R^1	R	Cpd.	R^1	R
6a	H	*i*-Pr	**6d**	Me	Et
6b	Me	*i*-Pr	**6e**	H	Me
6c	H	Et	**6f**	Me	Me

Scheme 5



with di-isopropyl phosphite (**7a**) in refluxed toluene in the presence of triethylamine (TEA). Similar treatment of **1a,b** with dialkyl phosphite **7b,c** afforded α-hydroxyphosphonates **6c–f** (Scheme 4).

Conversely, *o*-azidoquinolinecarbaldehydes **1a,b** react with tris(dimethylamino)phosphine **8** in dry tetrahydofuran (THF) at r.t. (24 h) to give triazenylidene-phosphoranes **9a,b** as a water-sensitive fine powder, quite stable for few days in a desiccator (Scheme 5-i). When a protonating agent (e.g., 2 mL of H_2O) is present in the reaction medium, the reaction is markedly accelerated leading to the formation of azaphospholes **12a,b** (~80%). Obviously, compounds **12a,b** were formed through the initial formation of the phosphineimines **10a,b**, followed by quenching a molecule of H_2O to give the intermediates **11** with concomitant loss of dimethylamine ($HNMe_2$). Stabilization of **11** *via* extrusion of another mole of dimethylamine resulted in the formation of the azaphospholes **12a** and **12b** (Scheme 5-ii).

Furthermore, the behavior of compounds **1a,b** toward the active Horner–Emmons reactant, tetraethyl methylenebisphosphonate (**13**) was next investigated. A mixture of 1.3 equivalent of **13** and *o*-azidocarbaldehydes **1a,b** in alcoholic sodium ethoxide solution was stirred at room temperature for 6 h. After the usual workup, the respective ethane-1,1-ylide-diphosphonates **14a,b** (~73% yield) were isolated. The gem-diphosphonate structure **14** was delineated by IR, NMR and MS spectra. **14a** exhibited absorption bands due to the stretching vibrations of C=C, P—O—C, P=O and tetrazole ring at 1618, 1030, 1254 and 1180 cm^{-1}, respectively, in its IR spectra. The ^{31}P-NMR spectrum of **14a** showed a sharp singlet at δp (DMSO): 18.4 ppm. The ^{1}H and ^{13}C data are also in accord with the assigned structure (see the "EXPERIMENTAL" section). The formation of **14a,b** can be rationalized as occurring in Scheme 6 through the condensation of **13** with the aldehydic-carbonyl group and extrusion of a molecule of H_2O (Perkin-type condensation). Perkin reaction has been previously described for a similar reaction of the bisphosphonate **13** with aldehydes [24]. Ethylidenebis-phosphonates and the relevant phosphonic acids belong to an important class of compounds used for the treatment of bone diseases, such as osteoporosis, hypocalcemia, inflammation, and rheumatoid arthritis [25,26].

PHARMACOLOGY

The prospective potency of our products for treating the inflammatory disease was based on the results of the prediction that had been carried out, in the earlier stage. The CAMM and PASS program was adopted for designing—*in silico*—the structures of potentially active molecules for future synthesis.

Anti-inflammatory screening. An initial evaluation of anti-inflammatory activity of the synthesized compounds **5a–f**, **6a–f**, **12a,b**, and **14a,b** as well as the substrates **1a** and **1b**, was determined *in vivo* by the acute carrageenin-induced paw edema standard method in rats [27,28]. Carrageenin, which is a sulfated polysaccharide, extracted from sea weed has been extensively used to induce inflammation in a number of animal species. Furthermore, the carrageenin-induced rat hind paw edema is now routinely used for the assay of anti-inflammatory agents. The reproducibility and the fact that the edema depends entirely on a local inflammatory reaction devoid of antigenic properties has made carrageenin a most widely used phlogistic agent in experimental pharmacology, and a good correlation has been shown to exist between the antiphlogistic and anti-inflammatory effects of several drugs.

In all experiments, carrageenin was administered into the left hind paw. Anti-inflammatory activity of the synthesized compounds **5a–f**, **6a–f**, **12a,b**, and **14a,b** as well as **1a** and **1b** (at a dose 50 mg/kg body weight) was measured at successive time intervals (1, 2, and 4 h after carrageenin injection) and compared with that of indomethacin at the same dose, which was used as a reference standard (Table 1). However, when the rats were reused, carrageenin injection was given into the right hind paw (Figs. 1 and 2).

The recorded data in Table 1 show that 12 of 16 newly synthesized compounds have moderate to good anti-

Scheme 6

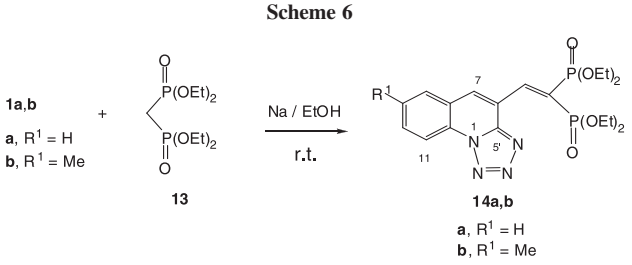


Table 1

Anti-inflammatory activity of new products **5a-f**, **6a-f, 12a,b, 14a,b**, and **1a,b** in acute carrageenin induced paw edema in rats.

Compound	Mean swelling[a] volume (mL; percentage inhibition of edema)			Potency[d] (%)
	1 h	2 h	4 h	
Control	0.568 ± 0.192[c] (00.0)	0.649 ± 0.067[c] (00.0)	0.869 ± 0.058[c] (00.0)	–
A[b]	0.272 ± 0.011[c] (52.1)	0.354 ± 0.015[c] (45.4)	0.442 ± 0.034[c] (49.1)	100
5a	0.278 ± 0.028[c] (51.0)	0.368 ± 0.031[c] (43.3	0.460 ± 0.038[c] (47.0)	95.7
5b	0.286 ± 0.033[c] (49.6)	0.372 ± 0.067[c] (42.6)	0.472 ± 0.057[c] (45.6)	92.8
5c	0.558 ± 0.055[c] (8.8)	0.552 ± 0.092[c] (15.1)	0.750 ± 0.050[c] (13.7)	27.8
5d	0.322 ± 0.024[c] (43.3)	0.388 ± 0.059[c] (40.2)	0.532 ± 0.094[c] (38.7)	78.8
5e	0.364 ± 0.039[c] (35.9)	0.378 ± 0.102[c] (41.7)	0.502 ± 0.112[c] (42.2)	85.9
5f	0.588 ± 0.055[c] (8.8)	0.551 ± 0.092[c] (15.1)	0.784 ± 0.066[c] (9.8)	19.9
6a	0.422 ± 0.028[c] (25.7)	0.498 ± 0.062[c] (23.2)	0.725 ± 0.052[c] (16.5)	33.6
6b	0.495 ± 0.045[c] (12.9)	0.562 ± 0.077[c] (13.4)	0.742 ± 0.066[c] (14.6)	29.6
6c	0.392 ± 0.062[c] (31.0)	0.392 ± 0.055[c] (39.5)	0.557 ± 0.048[c] (35.9)	73.1
6d	0.408 ± 0.027[c] (28.2)	0.447 ± 0.076[c] (31.1)	0.566 ± 0.066[c] (34.8)	70.8
6e	0.338 ± 0.055[c] (40.4)	0.442 ± 0.062[c] (31.8)	0.538 ± 0.048[c] (38.0)	77.4
6f	0.347 ± 0.034[c] (38.9)	0.444 ± 0.062[c] (31.5)	0.586± 0.079[c](32.5)	66.2
12a	0.247 ± 0.032[c] (56.5)	0.326 ± 0.039[c] (49.7)	0.436 ± 0.048[c] (49.8)	101.4
12b	0.256 ± 0.026[c] (54.9)	0.317 ± 0.037[c] (51.1)	0.425 ± 0.045[c] (51.0)	103.9
14a	0.211 ± 0.025[c] (62.8)	0.297 ± 0.032[c] (54.2)	0.403± 0.030[c] (53.6)	109.2
14b	0.228 ± 0.023[c] (59.8)	0.308 ± 0.024[c] (52.5)	0.401± 0.033[c] (53.8)	109.6
1a	0.510 ± 0.034[c] (12.3)	0.552 ± 0.092[c] (15.1)	0.818 ± 0.079[c] (9.8)	11.8
1b	0.558 ± 0.055[c] (8.8)	0.562 ± 0.077[c] (13.4)	0.830 ± 0.050[c] (5.0)	10.2

SEM, standard error of the mean.
[a]Data are means of two independent determinations at least, and the deviation in absorbance values was less than 10%.
[b]**A,** Indomethacin (used as a reference standard), each value represents the mean ± of two independent experiments with six animals in each group.
[c]Statistical significance of results was established using the Student's test from the standard at $P < 0.05$.
[d]Potency was expressed as percentage edema inhibition of the tested compounds relative to percentage edema inhibition of **A** at 4-h effect.

inflammatory properties when compared with the available indomethacin-drug, without toxic side effect. The bisphosphonates **14a**, **14b** and the azaphospholes **12a**, **12b** possess maximum inhibitory effect at all detected time intervals when compared with the standard group. Nevertheless, the substrates **1a**, **1b**, and the monophosphonates ($P(O)(O^iPr)_2$): **5c, 5f,** and **6a,b** showed poor effect as anti-inflammatory agents. Other compounds, that is **6c–f, 5a, 5b, 5d,** and **5e** have displayed moderate to good effects on inhibitory properties, especially at 1 h.

Structure–activity correlation based on the obtained results indicates that the bisphosphonate compounds **14a** and **14b** showed the highest anti-inflammatory activity, which is in accord to other similar studies in the literature [25,26].

Additionally, it has been also noticed that substitution of quinoline-3-carboxyaldehyde with a methyl group at the 6-position reduced the observed anti-inflammatory activity (i.e., **5d** < **5a**). On the other hand, it has been observed that the phosphor esters with a methoxy group (i.e., **5a** and **6e**) improved the observed anti-inflammatory activities compared with the case of using an ethoxy group as observed in compounds **5b** and **6c**. Similar result is hold for *iso*-propoxy group, which explains the role of the alkoxy-phosphor ester length in reflecting the pharmacological properties: *i*-PrO < EtO < MeO.

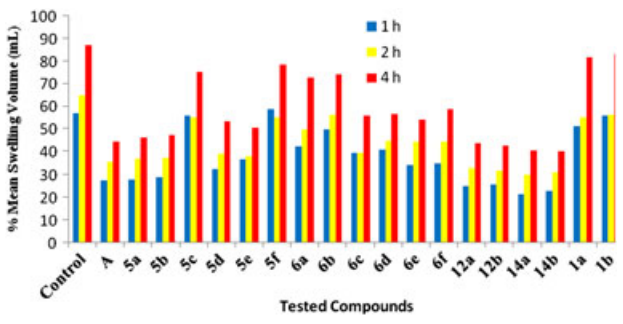


Figure 1. Mean edema volume (mL) of the compounds at successive time intervals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

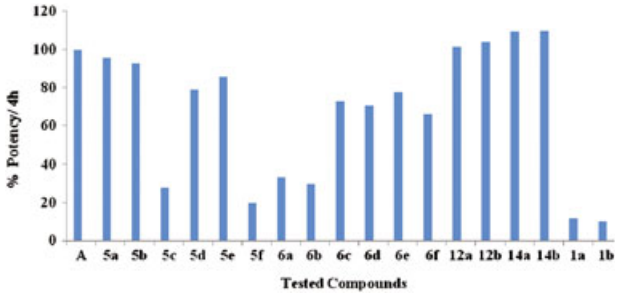


Figure 2. Anti-inflammatory activity potency (after 4 h) of the tested compounds relative to indomethacin which was used as a reference standard. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Toxicity of the promised products. Toxicological studies of the most promisingly synthesized anti-inflammatory active compounds **12a** and **14a** were performed using medium lethal dose, 50%, (LD_{50}) standard method in mice in 500, 750, and 1000 mg/kg (body weight), i.e., 10- to 20-fold of the used anti-inflammatory effective dose. However, no toxic symptoms or mortality rates were observed after 24 h postadministrations explaining the safe behavior of the used doses.

CONCLUSION

In conclusion, we were successful in synthesizing a variety of phosphorylated tricyclic system in good to excellent yields, without toxic side effects. The convenience and novelty of this work is reflected in its several advantages, such as mild reaction conditions, short reaction time, and easy workup procedure, without the need to chromatographic purification. The investigation showed that notwithstanding 2-azidoquinolines **1a** and **1b** react mainly in the tautomeric tetrazole-form (Schemes , 2–4 and 6), the involvement of the azido group in some reactions was also occurred (Scheme 5), which reflects the versatility of the azido group and the phosphorus reagents as well.

EXPERIMENTAL

General. Melting points were determined with open capillary tube on an electrothermal (variable heater) melting point apparatus and were uncorrected. IR spectra were recorded on a PerkinElmer spectrophotometer model 297 using KBr disc. NMR spectra were measured with a JEOL E.C.A-500 MHz (^{13}C: 125.7 MHz, ^{1}H: 500 MHz, ^{31}P: 202.4 MHz) spectrometer. ^{31}P-NMR spectra were recorded with H_3PO_4 (85%) as external reference. ^{1}H- and ^{13}C-NMR spectra were recorded with trimethylsilane as internal standard in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are given in ppm. The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. All international principles and local regulations concerning the care and use of laboratory animals were considered during the pharmacological screening.

Preparation of 2-azidoquinolines-3-carbaldehyde 1a,b. To a solution of (26 mmol) of 2-chloroquinoline-3-carbaldehyde (4.98 g) or 2-chloro-6-methylquinoline-3-carbaldehyde (5.35 g) in 15 mL of DMSO, 2 g of sodium azide (30 mmol) was added, and the resulting mixture was heated at 90°C for 4 h. The precipitated product was collected, washed with acetone, and dried to give **1a** and **1b**, respectively.

*2-Azidoquinoline-3-carbaldehyde (**1a**).* This compound was obtained as straw yellow crystals 4.12 g (80%); mp 260–262°C (lit. [21]: mp 260°C).

*2-Azido-6-methylquinoline-3-carbaldehyde (**1b**).* This compound was obtained as orange crystals, 4.25 g (77%); mp 235–236°C; IR: ν_{max} C=O 1699, N_3 2105 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.54 (s, 3H, 6-Ar-CH_3), 7.66 (d, J_{H-H} = 6.6 Hz, 1H, 7-CH), 7.82 (s, 1H, 5-CH), 8.02 (d, J_{H-H} = 6.6 Hz, 8-CH), 8.66 (s, 1H, 4-CH), 10.72 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$): δ 182.6 (C=O), 153.5 (9-C), 148.6 (2-CN_3), 129.5 (4-C), 136.8, 132.5, 129.8, 128.2, 125.7, (7-C, 5-C, 6-C, 8-C, 10-C,), 112.3 (3-C), 20.9 (6-C-*C*H_3); EI-MS: *m/z* (%): 212 [M^+](15), 184 [M^+–N_2] (57), 170 [M^+–N_3] (100). Anal. Calcd for $C_{11}H_8N_4O$ (212.2): C, 62.26; H, 3.80; N, 26.40. Found: C, 62.34; H, 3.85; N, 26.46.

Reactions of 2-azidoquinolines-3-carbaldehyde 1a,b with trimethyl- (3a) and triethyl phosphites (3b). Preparation of compounds 5a,b,d,e. To a solution of (4 mmol) of the azide (**1a**, 0.79 g or **1b**, 0.85 g) in 25 mL of dry toluene at 0°C (5.2 mmol) of freshly distilled **3a** or **3b** was added dropwise with stirring. After the addition was complete, the reaction mixture was refluxed for ≈4–6 h (thin layer chromatography (TLC)), and the solvent was evaporated to dryness. The residue was washed several times with light petroleum (40–60°C), and crystallized from the proper solvent to give **5a,b** (from **1a** and **3a,b**) or **5d,e** (from **1b** and **3a,b**), respectively.

*Dimethyl [methoxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**5a**).* This compound was obtained as light orange needles, 1.03 g (80%); mp 218–220°C (MeCN); IR: ν_{max} P—O, free 1256, tetrazole 1185, P—O—C 1036 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.84 (d, $^{4}J_{P-H}$ = 3.7 Hz, 3H, H_3COC), 3.97 (d, $^{3}J_{P-H}$ = 11.4 Hz, 6H, H_3COP), 5.75 (d, $^{2}J_{P-H}$ = 18.8 Hz, 1H, HC-P), 7.90–8.12 (2m, 2H, 9- and 10-HAr), 8.45 (s, 1H, 7-HAr), 8.56, 8.75 (2d, J_{H-H} = 6.8 Hz, 2 × 1H, 8-, 11-HAr); ^{13}C-NMR δ ($CDCl_3$): 133.8 (d, $^{3}J_{P-C}$ = 8.6 Hz, C-5), 130.9 (d, $^{2}J_{P-C}$ = 14.7 Hz, 6-C), 124.6 (d, $^{3}J_{P-C}$ = 8.4 Hz, 7-C), 139.5, 134.8, 130.1, 128.6, 123.5, 114.7 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 79.8 (d, $^{1}J_{P-C}$ = 144 Hz, P-C), 62.0 (d, $^{3}J_{P-C}$ = 8.4 Hz, *C*H_3OC), 54.2 (d, $^{2}J_{P-C}$ = 13.8 Hz, CH_3OP); ^{31}P-NMR ($CDCl_3$): δ 26.8; EI-MS: *m/z* (%): 322 [M^+] (8), 306 (17), 284 (26), 257 (28), 186 (15), 129 [33, C_9H_6N], 109 [100, P(O)(OMe)$_2$]. Anal. calcd for $C_{13}H_{15}N_4O_4P$ (322.3): C, 48.45; H, 4.69; N, 17.39; P, 9.61. Found: C, 48.53; H, 4.71; N, 17.32; P, 9.71.

*Diethyl [ethoxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**5b**).* This compound was obtained as yellow crystals, 1.19 g (82%); mp 210–212°C ($CHCl_3$); IR: ν_{max} P—O, free 1261, tetrazole 1160, P—O—C 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.99 (t, J_{H-H} = 6.5 Hz, 3H, $H_3C.CO$), 1.28 (dt, J_{H-H} = 6.6, $^{4}J_{P-H}$ = 3.8 Hz, 6H, $H_3C.COP$), 3.9 (dq, J_{H-H} = 6.5, $^{4}J_{P-H}$ = 2.5 Hz, 2H, $H_2C.CO$), 4.08 (dq, J_{H-H} = 6.6, $^{3}J_{P-H}$ = 5.2 Hz, 4H, H_2COP), 5.58 (d, $^{2}J_{P-H}$ = 21.2 Hz, 1H, HC-P), 7.89, 8.13 (2m, 2 × 1H, 9- and 10-HAr), 8.43 (s, 1H, 7-HAr), 8.66, 8.78 (2d, J_{H-H} = 8.2 Hz, 2 × 1H, 8-, 11-HAr); ^{13}C-NMR ($CDCl_3$): δ 132.4 (d, $^{3}J_{P-C}$ = 8.6 Hz, 5-C), 130.8 (d, $^{2}J_{P-C}$ = 14.7 Hz, 6-C), 124.8 (d, $^{3}J_{P-C}$ = 8.4 Hz, 7-C), 140.2, 136.6, 135.4, 128.3, 122.8, 114.7 (12-, 13-, 10-, 8-, 9-, 11-CAr), 79.8 (d, $^{1}J_{P-C}$ = 167 Hz, P-C), 65.0 (d, $^{3}J_{P-C}$ = 8.4 Hz, *C*H_2OC), 62.2 (d, $^{2}J_{P-C}$ = 11.4 Hz, CH_2OP), 16.8 (d, $^{3}J_{P-C}$ = 9.2 Hz, *C*H_3C.OP), 15.7 (*C*H_3C.O); ^{31}P-NMR ($CDCl_3$): δ 27.2 ppm; EI-MS: *m/z* (%): 364 [M^+] (7), 332 (25), 308 (33), 273 (61), 258 (52), 155 (27), 138 [100, P(O)(OEt)$_2$], 135.3 (88), 129 [57, C_9H_6N]. Anal. calcd for $C_{16}H_{21}N_4O_4P$ (364.3): C, 52.75; H, 5.81; N, 15.38; P, 8.50. Found: C, 52.83; H, 5.88; N, 15.31; P, 8.55.

*Dimethyl [methoxy(9-methyltetrazolo[1,5-a]quinolin-6-yl) methyl]phosphonate (**5d**).* This compound was obtained as yellow crystals, 1.13 g (84%); mp 196–198°C (EtOH); IR: ν_{max} P—O, free 1258, tetrazole 1177, P—O—C 1055 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.22 (s, 3H, H_3C-9Ar), 2.78 (d, $^{4}J_{P-H}$ = 4.7 Hz, 3H, H_3CO), 3.85 (d, $^{3}J_{P-H}$ = 10.5 Hz, 6H, H_3COP), 5.48 (d, $^{2}J_{P-H}$ = 17.6 Hz, 1H, HC-P), 7.82, 7.99 (2s, 2 × 1H, 7- and 8-H-Ar), 7.82, 7.94 (2d, J_{H-H} = 8.4 Hz, 2×1H, 10- and 11-HAr); ^{13}C-NMR ($CDCl_3$): δ 135.5 (d, $^{3}J_{P-C}$ = 7.5 Hz, 5-C), 130.6 (d, $^{2}J_{P-C}$ = 17 Hz, 6-C), 126.4 (d, $^{3}J_{P-C}$ = 6.4 Hz, 7-C), 141.0, 136.2, 132.3,

126.9, 126.0, 117.8 (12-, 10-, 9-, 8-, 13-, 11-CAr), 78.9 (d, $^1J_{P-C}$ = 136 Hz, C-P), 62.2 (d, $^3J_{P-C}$ = 6.4 Hz, *C*H_3OC), 52.8 (d, $^2J_{P-C}$ =10.5 Hz, CH_3OP), 20.8 (CH_3-9Ar); ^{31}P-NMR ($CDCl_3$): δ 28.4; EI-MS: *m/z* (%): 336 [M^+] (15), 322 (28), 306 (27), 284 (36), 257 (68), 186 (55), 129 [44, C_9H_6N], 109 [100, P(O)$(OMe)_2$]. Anal. calcd for $C_{14}H_{17}N_4O_4P$ (336.3): C, 50.00; H, 5.10; N, 16.66; P, 9.21. Found: C, 50.09; H, 5.18; N, 16.62; P, 9.26.

*Diethyl [ethoxy(9-methyltetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**5e**).* This compound was obtained as yellow crystals, 1.32 g (87%); mp 184–185°C ($CHCl_3$); IR: ν_{max} P—O, free 1254, tetrazole 1185, P—O—C 1086 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22–1.26 (m (2 × dt), 3H and 6H, H_3C.CO and H_3C.COP), 2.32 (s, 3H, H_3C-9Ar), 3.53 (dq, J_{H-H} = 6.5, $^4J_{P-H}$ = 2.5 Hz, 2H, H_2CO), 4.08 (dq, J_{H-H} = 6.6, $^3J_{P-H}$ = 5.2 Hz, 4H, H_2COP), 5.58 (d, $^2J_{P-H}$ = 20.7 Hz, 1H, HC-P), 7.80, 7.98 (2s, 2 × 1H, 7- and 8-H-Ar), 7.84, 7.96 (2d, J_{H-H} = 8.4 Hz, 2 × 1H, 10- and 11-HAr); ^{13}C-NMR ($CDCl_3$): δ 133.0 (d, $^3J_{P-C}$ = 8.2 Hz, 5-CAr), 130.9 (d, $^2J_{P-C}$= 14.7 Hz, 6-CAr), 124.6 (d, $^3J_{P-C}$ = 8.4 Hz, 7-CAr), 139.5, 134.8, 130.1, 128.6, 123.5, 113.7 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 79.8 (d, $^1J_{P-C}$ = 144 Hz, P-C), 62.0 (d, $^3J_{P-C}$ = 8.4 Hz, *C*H_3OC), 54.2 (d, $^2J_{P-C}$ = 13.8 Hz, CH_3OP). 63.7 (d, $^3J_{P-C}$ = 7.4 Hz, *C*H_2OC), 61.8 (d, $^2J_{P-C}$ = 12.5 Hz, CH_2OP), 20.4 (CH_3-9Ar), 16.4 (d, $^3J_{P-C}$ = 9.2 Hz, *C*H_3C·OP), 15.8 (*C*H_3C·O); ^{31}P-NMR ($CDCl_3$): δ 26.2 ppm; EI-MS: *m/z* (%): 378 [M^+] (15), 363(13), 333 (53), 272 (17), 268 (11), 184 (78), 138 [100, P(O)$(OEt)_2$], 135.3 (88), 129 [57, C_9H_6N]. Anal. calcd for $C_{17}H_{23}N_4O_4P$ (378.4): C, 53.96; H, 6.13; N, 14.81; P, 8.19. Found: C, 54.03; H, 6.22; N, 14.83; P, 8.23.

Reactions of 1a,b with triisopropyl phosphite (3c). Preparation of 5c, 5f, and 6a,b. Compound **1a** or **1b** (4 mmol) in 25 mL of dry toluene was treated with 5.2 mmol of freshly distilled **3c**. The reaction mixture was heated under reflux for 4 h and the solvent was evaporated under vacuum to dryness. The residue was washed several times with light petroleum (40–60°C). Fractional crystallization from toluene afforded first **5c** or **5f**. Crystallization of the residue from MeCN afforded **6a** or **6b**, respectively.

*Diisopropyl [isopropoxy(tetrazolo[1,5-a]quinolin-6-yl) methyl]phosphonate (**5c**).*. This compound was obtained as yellow crystals, 729 mg (45% yield); mp 232–234°C (toluene); IR: ν_{max} P—O, free 1254, tetrazole 1182, P—O—C 1110 cm^{-1}; ^{1}H-NMR (DMSO-d_6]: δ 1.01 (d, J_{H-H} = 7.2, 6H, *iso*-(*H*$_3$C)$_2$HCO), 1.13, 1.26 (2dd, J_{H-H} = 7.2, $^4J_{P-H}$ = 5.5 Hz, 12H, [*iso*-$(H_3C)_2$C·O]$_2$P), 4.12 (sept, J_{H-H} = 7.2, $^4J_{P-H}$ = 2.4 Hz, 1H, HCOC), 4.64 (d.sept, J_{H-H} = 7.2, $^3J_{P-H}$ = 6.4 Hz, 2H, HCOP), 5.62 (d, $^2J_{P-H}$ = 22.2 Hz, 1H, HC-P), 7.89, 8.03 (2m, 2 × 1H, 10- and 9-HAr), 8.13 (s, 1H, 7-HAr), 8.64, 8.76 (2d, J_{H-H} = 8.2 Hz, 2 × 1H, 8-, 11-HAr); ^{13}C-NMR (DMSO-d_6): δ 134.7 (d, $^3J_{P-C}$ = 8.2 Hz, C-5), 130.5 (d, $^2J_{P-C}$ = 12.7 Hz, 6-C), 125.4 (d, $^3J_{P-C}$= 8.8 Hz, 7-C-Ar), 139.8, 136.4, 129.1, 126.6, 123.6, 113.9 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 81.4 (d, $^1J_{P-C}$ = 154.4 Hz, C-P), 71.2 (d, $^2J_{P-C}$ = 12.8 Hz, CHOP), 68.0 (d, $^3J_{P-C}$ = 5.8 Hz, *C*HCO), 24.1 (d, $^3J_{P-C}$ = 4.6 Hz, *C*H_3CHOP), 22.3 (*C*H_3C.O); ^{31}P-NMR (DMSO-d_6): δ 26.8 ppm; EI-MS: *m/z* (%): 407 [M^++1] (15), 364 (13), 333 (22), 274 (18), 259 (48), 229 (55), 166 [100, P(O)$(OCMe_2)_2$], 129 [33, C_9H_6N]. Anal. calcd for $C_{19}H_{27}N_4O_4P$ (406.4): C, 56.15; H, 6.70; N, 13.39; P, 7.62. Found: C, 56.22; H, 6.75; N, 13.32; P, 7.70.

*Diisopropyl [isopropoxy(9-methyltetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**5f**).* This compound was obtained as orange crystals, 808 mg (48%); mp 203–205°C (toluene); IR: ν_{max} P—O, free 1260, tetrazole 1188, P—O—C 1081 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.03 (d, J_{H-H} = 6.4, 6H, (H_3C)$_2$HCO), 1.25, 1.28 (2dd, J_{H-H} = 6.4, $^4J_{P-H}$ = 6.5 Hz, 12H, [*iso*-$(H_3C)_2$C·O]$_2$P), 2.24 (s, 3H, H_3C-9Ar), 4.12 (d.sept, J_{H-H} = 6.5, $^4J_{P-H}$ = 2.6 Hz, 1H, HCC·O), 4.64 (d.sept, J_{H-H} = 6.5, $^3J_{P-H}$ = 8.4 Hz, 2H, HCOP), 5.62 (d, $^2J_{P-H}$ = 22.2 Hz, 1H, HC-P), 7.95 (s, 7-HAr), 7.89, 8.03 (2m, 2 × 1H, 10- and 11-HAr), 8.10 (s, 8-HAr);^{13}C-NMR ($CDCl_3$): δ 133.8 (d, $^3J_{P-C}$ = 8.6 Hz, C-5), 131.7 (d, $^2J_{P-C}$ = 13.8 Hz, 6-C), 126.7 (d, $^3J_{P-C}$ = 8.2 Hz, 7-C), 139.8, 134.3, 132.3, 128.6, 125.5, 116.7 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 79.4 (d, $^1J_{P-C}$ = 182.8 Hz, CH-P), 73.2 (d, $^2J_{P-C}$ = 11.8 Hz, CHOP), 70.6 (d, $^3J_{P-C}$ = 10.8 Hz, CHOC), 25.2 (d, $^3J_{P-C}$ = 4.6 Hz, *C*H_3C·OP), 22.3 (*C*H_3C·O), 20.7 (CH_3-9Ar); ^{31}P-NMR ($CDCl_3$): δ 26.7 ppm; EI-MS: *m/z* (%): 421 [M^++1] (18), 378 (16), 333 (11), 288 (28), 259 (68), 273 (44), 229 (62), 166 [100, P(O)$(OCMe_2)_2$], 129 [37, C_9H_6N]. Anal. calcd for $C_{20}H_{29}N_4O_4P$ (420.4): C, 57.13; H, 6.95; N, 13.33; P, 7.37. Found: C, 57.21; H, 7.03; N, 13.27; P, 7.42.

*Diisopropyl [hydroxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**6a**).* This compound was obtained as orange crystals, 159 mg (11%); mp 244°C (MeOH); IR: ν_{max} OH 3345, P—O, bonded 1240, tetrazole 1186, P—O—C 1035 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.11, 1.24 (2dd, J_{H-H} = 6.2 Hz, $^4J_{P-H}$ = 5.5 Hz, 12H, [*iso*-$(H_3C)_2$C·O]$_2$P), 4.44 (d. sept, J_{H-H} = 6.4, $^3J_{P-H}$ = 5.4 Hz, 2H, HCOP), 5.98 (d, $^2J_{P-H}$ = 21.6 Hz, 1H, HC-P), 7.84, 8.05 (2m, 2 × 1H, 10- and 9-HAr), 8.23 (s, 1H, 7-HAr), 8.44, 8.68 (2d, J_{H-H} = 8.2 Hz, 2 × 1H, 8- and 11-HAr), 9.58 (s.br, 1H, OH, exchang. with D_2O); ^{13}C-NMR (DMSO-d_6): δ 136.4 (d, $^3J_{P-C}$ = 8.5 Hz, C-5), 133.2 (d, $^2J_{P-C}$ = 14.7 Hz, 6-C), 124.8 (d, $^3J_{P-C}$ = 10.8 Hz, 7-C-Ar), 140.1, 136.4, 128.3, 125.6, 124.3, 113.6 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 74.4 (d, $^1J_{P-C}$ = 168.8 Hz, C-P), 71.2 (d, $^2J_{P-C}$ = 14.8 Hz, CHOP), 24.1 (d, $^3J_{P-C}$ = 4.6 Hz, *C*H_3CHOP); ^{31}P-NMR (DMSO-d_6): δ 24.8 ppm; EI-MS: *m/z* (%): 365 [M^++1] (22), 333 (14), 274 (31), 259 (50), 229 (52), 166 [100, P(O)$(OCMe_2)_2$], 129 [42, C_9H_6N]. Anal. calcd for $C_{16}H_{21}N_4O_4P$ (364.4): C, 52.75; H, 5.81; N, 15.38; P, 8.50. Found: C, 52.67; H, 5.77; N, 15.40; P, 8.43.

*Diisopropyl [hydroxy(9-methyltetrazolo[1,5-a]quinolin-6-yl) methyl] phosphonate (**6b**).* This compound was obtained as yellow crystals, 152 mg (10%); mp 211–213°C (MeOH); IR: ν_{max}, OH 3335, P—O, bonded 1228, tetrazole 1176, P—O—C 1105 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.24, 1.28 (2dd, J_{H-H} = 6.4, $^4J_{P-H}$ = 6.4 Hz, 12H, [*iso*-$(H_3C)_2$C·O]$_2$P), 2.26 (s, 3H, H_3C-9Ar), 4.28 (d.sept, J_{H-H} = 6.2, $^3J_{P-H}$ = 7.6 Hz, 2H, HCOP), 6.02 (d, $^2J_{P-H}$ = 22.4 Hz, 1H, HC-P), 7.95 (s, H-8Ar), 7.89, 8.03 (2d, J_{H-H} = 6.5, 2 × 1H, 10- and 11-HAr), 8.10 (s, 1H, 7-H), 9.63 (s.br, 1H, OH, exchang. with D_2O); ^{13}C-NMR (DMSO-d_6): δ 136.3 (d, $^3J_{P-C}$ = 8.5 Hz, C-5), 131.8 (d, $^2J_{P-C}$ = 14.4 Hz, 6-C), 126.6 (d, $^3J_{P-C}$ = 8.2 Hz, 7-C), 141.2, 134.3, 132.6, 126.8, 122.6, 116.2 (12-, 10-, 13-, 8-, 9-, 11-C-Ar), 73.4 (d, $^1J_{P-C}$ = 177 Hz, CH-P), 61.6 (d, $^3J_{P-C}$ = 10.8 Hz, CHOP), 20.3 (CH_3-9Ar), 16.6 (d, $^3J_{P-C}$ = 8.6 Hz, *C*H_3CHOP); ^{31}P-NMR (DMSO-d_6): δ 23.8 ppm; EI-MS: *m/z* (%): 379 [M^++1] (20), 333 (14), 288 (30), 273 (65), 259 (66), 229 (36), 166 [100, P(O)$(OCMe_2)_2$], 129 [42, C_9H_6N]. Anal. calcd for $C_{17}H_{23}N_4O_4P$ (378.4): C, 53.96; H, 6.13; N, 14.81; P, 8.19. Found: C, 53.88; H, 6.06; N, 14.74; P, 8.27.

The reaction of 2-azidoquinolines-3-carbaldehyde 1a,b with dialkyl phosphites 7a–c. Preparation of compounds 6a–f. A mixture of (4 mmol) of (**1a**, 0.79 g or **1b**, 0.85 g) and 5.2 mmol of diisopropyl (**7a**), diethyl (**7b**) or dimethyl phosphite (**7c**) was refluxed in 25 mL dry toluene containing 0.7 mL TEA for ≈6–10 h (TLC). The solvent was evaporated under vacuum to dryness, followed by washing the residue several times with light petroleum (40–60°C), and crystallization from the proper solvent to give **6a–f**, respectively.

*Diisopropyl [hydroxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**6a**).* This compound was obtained as orange crystals, 1.36 g (94%), which was identical with the product previously obtained (TLC, IR, and MS spectra).

*Diisopropyl [hydroxy(9-methyltetrazolo[1,5-a]quinolin-6-yl) methyl] phosphonate (**6b**).* This compound was obtained as orange crystals, 1.32 mg (87%), which was identical with the product previously obtained (TLC, IR, and MS spectra).

*Diethyl [hydroxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**6c**).* This compound was obtained as yellow crystals, 1.15 g (86%); mp 225–228°C (EtOH); IR: ν_{max} OH 3379, P—O, chelated 1228, tetrazole 1184, P—O—C 1085 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.32 (dt, J_{H-H} = 6.6, $^4J_{P-H}$ = 4.8 Hz, 6H, $H_3C{\cdot}COP$), 4.18 (dq, J_{H-H} = 6.8, $^3J_{P-H}$ = 5.7 Hz, 4H, H_2COP), 6.06 (d, $^2J_{P-H}$ = 20.4 Hz, 1H, HC-P), 7.91, 8.13 (2m, 2 × 1H, 10- and 9-HAr), 8.25 (s, 1H, 7-HAr), 8.56, 8.66 (2d, J_{H-H} = 8.2 Hz, 2 × 1H, 8-, 11-HAr), 9.66 (s.br, 1H, OH, exchang. with D_2O); ^{13}C-NMR (DMSO-d_6): δ 134.2 (d, $^3J_{P-C}$ = 8.8 Hz, 5-C), 136.6 (d, $^2J_{P-C}$ = 12.7 Hz, 6-C), 126.4 (d, $^3J_{P-C}$ = 8.4 Hz, 7-C), 139.9, 136.6, 135.8, 128.7, 125.8, 114.8 (12-, 13-, 10-, 8-, 9-, 11-CAr), 76.3 (d, $^1J_{P-C}$ = 148 Hz, C-P), 61.6 (d, $^2J_{P-C}$ = 10.4 Hz, CH_2OP), 16.6 (d, $^3J_{P-C}$ = 9.2 Hz, $CH_3C{\cdot}OP$); ^{31}P-NMR (DMSO-d_6): δ 25.4 ppm; EI-MS: *m/z* (%): 335 [M^+−1] (28), 308 (39), 273 (26), 258 (42), 155 (21), 138 [100, P(O)$(OEt)_2$], 135.3 (57), 129 [37, C_9H_6N]. Anal. calcd for $C_{14}H_{17}N_4O_4P$ (336.3): C, 50.00; H, 5.10; N, 16.66; P, 9.21. Found: C, 50.07; H, 5.08; N, 16.62; P, 9.29.

*Diethyl [hydroxy(9-methyltetrazolo[1,5-a]quinolin-6-yl) methyl]phosphonate (**6d**).* This compound was obtained as yellow crystals, 1.19 g (85%); mp 205–207°C (MeCN); IR: ν_{max} OH 3385, P—O, chelated 1224, tetrazole 1180, P—O—C 1065 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.24 (dt, J_{H-H} = 6.6, $^4J_{P-H}$ = 3.2 Hz, 6H, $H_3C.COP$), 2.32 (s, 3H, H_3C-9Ar), 4.08 (dq, J_{H-H} = 6.6, $^3J_{P-H}$ = 5.2 Hz, 4H, H_2COP), 6.08 (d, $^2J_{P-H}$ = 20.7 Hz, 1H, HC-P), 7.80, 7.98 (2s, 2 × 1H, 7- and 8-HAr), 7.84, 7.96 (2d, J_{H-H} = 8.4 Hz, 2 × 1H, 10- and 11-HAr), 9.36 (s.br, 1H, OH, exchang. with D_2O); ^{13}C-NMR (DMSO-d_6): δ 132.7 (d, $^3J_{P-C}$ = 7.8 Hz, C-5), 130.4 (d, $^2J_{P-C}$ = 15.6 Hz, 6-C), 126.4 (d, $^3J_{P-C}$ = 8.8 Hz, 7-CAr), 140.08, 134.6, 131.3, 128.2, 124.6, 116.4 (12-, 10-, 13-, 8-, 9-, 11-CAr), 73.9 (d, $^1J_{P-C}$ = 146 Hz, C-P), 61.5 (d, $^2J_{P-C}$ = 10.8 Hz, CH_2OP), 20.4 (CH_3-9Ar), 18.2 (d, $^3J_{P-C}$ = 8.8 Hz, $CH_3C.OP$); ^{31}P-NMR (DMSO-d_6): δ 24.7 ppm; EI-MS: *m/z* (%): 349 [M^+−1] (25), 321(30), 268 (18), 184 (48), 138 [100, P(O)$(OEt)_2$], 135.3 (58), 129 [25, C_9H_6N]. Anal. calcd for $C_{15}H_{19}N_4O_4P$ (350.3): C, 51.43; H, 5.47; N, 15.99; P, 8.84. Found: C, 51.51; H, 5.44; N, 15.94; P, 8.89.

*Dimethyl [hydroxy(tetrazolo[1,5-a]quinolin-6-yl)methyl] phosphonate (**6e**).* This compound was obtained as orange crystals, 1.03 g (84%); mp 240–242°C (acetone); IR: ν_{max} OH 3324, P—O, chelated 1228, tetrazole 1173, P—O—C 1080 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.88 (d, $^3J_{P-H}$ = 11.5 Hz, 6H, H_3COP), 6.05 (d, $^2J_{P-H}$ = 20.4 Hz, 1H, HC-P), 7.88, 8.18 (2m, 2 × 1H, 10- and 9-HAr), 8.47 (s, 1H, 7-HAr), 8.57, 8.77 (2d, J_{H-H} = 8.2 Hz, 2 × 1H, 8-, 11-HAr), 9.44 (s br, 1H, OH, exchang. with D_2O); ^{13}C-NMR (DMSO-d_6): δ 134.4 (d, $^3J_{P-C}$ = 8.6 Hz, C-5), 133.8 (d, $^2J_{P-C}$ = 14.7 Hz, 6-C), 124.4 (d, $^3J_{P-C}$ = 8.4 Hz, 7-C), 139.8, 136.4, 134.6, 127.6, 123.8, 113.4 (12-, 10-, 8-, 13-, 9-, 11-C-Ar), 74.8 (d, $^1J_{P-C}$ = 136 Hz, C-*P*), 52.5 (d, $^2J_{P-C}$ = 11.8 Hz, CH_3OP); ^{31}P-NMR (DMSO-d_6): δ 24.4 ppm; EI-MS: *m/z* (%): 308 [M^+] (6), 307 [M^+−1] (17), 284 (46), 257 (28), 186 (25), 129 [43, C_9H_6N], 109 [100, P(O)$(OMe)_2$]. Anal. calcd for $C_{12}H_{13}N_4O_4P$ (308.2): C, 46.76; H, 4.25; N, 18.18; P, 10.05. Found: C, 46.85; H, 4.19; N, 18.11; P, 10.11.

*Dimethyl [hydroxy(9-methyltetrazolo[1,5-a]quinolin-6-yl) methyl]phosphonate (**6f**).* This compound was obtained as orange crystals, 1.14 g (88%); mp 213–215°C (acetone); IR: ν_{max} OH 3340, P—O, bonded 1228, tetrazole 1180, P—O—C 1062 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.26 (s, 3H, H_3C-9-Ar), 3.88 (d, $^3J_{P-H}$ = 10.8 Hz, 6H, H_3COP), 6.04 (d, $^2J_{P-H}$ = 18.6 Hz, 1H, HC-P), 7.76, 7.88 (2s, 2 × 1H, 7- and 8-H-Ar), 7.82, 7.94 (2d, J_{H-H} = 8.4 Hz, 2 × 1H, 10- and 11-HAr), 9.56 (s br, 1H, OH, exchang. with D_2O); ^{13}C-NMR ($CDCl_3$): δ 135.6 (d, $^3J_{P-C}$ = 7.5 Hz, 5-C), 132.2 (d, $^2J_{P-C}$ = 14.3 Hz, 6-C), 126.8 (d, $^3J_{P-C}$ = 5.4 Hz, 7-C), 140.06, 136.1, 132.0, 126.8, 126.4, 116.7 (12-, 9-, 10-, 8-, 13-, 11-CAr), 74.8 (d, $^1J_{P-C}$ = 144 Hz, C-P), 54.2 (d, $^2J_{P-C}$ =10.5 Hz, CH_3OP), 20.6 (CH_3-9Ar); ^{31}P-NMR ($CDCl_3$): δ 24.2 ppm; EI-MS: *m/z* (%): 322 [M^+] (16), 321 [M^+−1] (23), 284 (31), 257 (36), 186 (65), 129 [80, C_9H_6N], 109 [100, P(O)$(OMe)_2$]. Anal. calcd for $C_{13}H_{15}N_4O_4P$ (322.2): C, 48.45; H, 4.69; N, 17.39; P, 9.61. Found: C, 48.54; H, 4.78; N, 17.34; P, 9.69.

The reaction of 1a,b with tris(dimethylamino)phosphine (8). Preparation of compounds 9a and 9b. Aminophosphine **8** (0.85 mL, 5.2 mmol) in 5 mL dry THF was added dropwise to **1a** (0.79 g, 4 mmol) or **1b** (0.85 g, 4 mmol) in 5 mL THF. The reaction mixture was stirred at r.t. for ≈24 h (TLC). The precipitate was collected and washed several times with light petroleum (40–60°C) to give **9a** and **9b**, respectively. Compounds **9a,b** are pure enough for carrying out the spectroscopic analyses and are stable for few days at −10°C.

*2-{3-[Tris(dimethylamino)phosphoranylidene]triaz-1-en-1-yl} quinoline-3-carbaldehyde (**9a**).* This compound was obtained as yellow material, 1.3 g (90%); mp 290–292°C; IR: ν_{max} C=O 1722, P=N 1355, [$P(NMe_2)_3$] 1335, 860 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.48, 2.63 (2d, $^3J_{P-H}$ = 10.8 Hz, 18H, $PN(CH_3)_2$), 7.34, 7.77 (2d, J_{H-H} = 7.8 Hz, 2 × 1H, 5- and 8-HAr), 8.02–8.36 (2m, 2 × 1H, 6- and 7-HAr), 8.55 (s, 1H, 4-HAr), 10.2 (s (br), 1H, HC=O); ^{13}C-NMR ($CDCl_3$): δ 184.3 (C=O), 155.8 (2-CAr), 132.3 (4-CAr), 111.7 (3-CAr), 150.6, 135.8, 132.3, 129.6, 125.4, 124.7 (9-, 5-, 7-, 10-, 8-, 6-CAr), 38.2 (d, $^2J_{P-C}$ = 28 Hz, P[N$(CH_3)_2]_3$); ^{31}P-NMR ($CDCl_3$): δ 38.6 ppm; EI-MS: *m/z* (%): 362 [M^++1] (13), 333 (21), 170 [M^+−91(N2 + $Me_2N)_3$P)] (100). Anal. calcd for $C_{16}H_{24}N_7OP$ (361.4): C, 53.18; H, 6.69; N, 27.13; P, 8.57. Found: C, 53.09; H, 6.66; N, 27.06; P, 8.63.

*6-Methyl-2-{3-[tris(dimethylamino)phosphoranylidene]triaz-1-en-1-yl}quinoline-3-carbaldehyde (**9b**).* This compound was obtained as an orange substance, 1.35 g (90%); mp 276–278°C; IR: ν_{max} C=O 1718, P=N 1360, [$P(NMe_2)_3$] 1322, 855 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.45, 2.64 (2d, $^3J_{P-H}$ = 10.8 Hz, 18H, $PN(CH_3)_2$), 2.55 (s, 3H, H_3C-6-Ar), 7.55 (s, 1H, 5-HAr), 7.97, 7.66 (2d, J_{H-H} = 6.5 Hz, 2 × 1H, 7-, 8-HAr), 8.68 (s, 4-HAr), 10.26 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$): δ 183.8 (C=O), 155.3 (2-CAr), 131.7 (4-C), 111.4 (3-C), 149.4, 136.8, 131.5, 130.7, 123.4 (9-, 7-, 6-, 5-, 8-, 10-CAr), 38.5 (d, $^2J_{P-C}$ = 30.2 Hz, P[$N(CH_3)_2]_3$), 20.6 (CH_3-Ar); ^{31}P-NMR ($CDCl_3$): δ 40.3 ppm; EI-MS: *m/z* (%): 376 [M^++1] (17), 347 (21), 184 [M^+−191, (N_2 + $Me_2N)_3$P)] (100). Anal. calcd for $C_{17}H_{26}N_7OP$ (375.4): C, 54.39; H, 6.98; N, 26.12; P, 8.25. Found: C, 54.45; H, 6.89; N, 26.05; P, 8.15.

The reaction of 1a,b with aminophosphine 8 in the presence of a protonating agent. Preparation of compounds 12a and 12b. Aminophosphine **8** (0.85 mL, 5.2 mmol) in 10 mL of THF was added in one portion to a mixture of 4 mmol of the azide (**1a**, 0.79 g or **1b**, 0.85 g) and 2 mL of H_2O in 10 mL THF. The reaction mixture was heated under reflux 2 h. The solvent was

evaporated to dryness; the residue was washed several times with cyclohexane and crystallized from the proper solvent to give **12a** and **12b**, respectively.

*2-(Dimethylamino)-1,2-dihydro-3H-[1,2]azaphospholo[5,4-b] quinoline-3-one 2-oxide (**12a**).* This compound was obtained as yellow crystals, 0.8 g (77%); mp 172–174°C (CH_2Cl_2); IR: ν_{max} NH 3405, C=O 1728, P—O 1256, P-NR 1320, 838 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.88 (d, $^3J_{P-H}$ = 10.4 Hz, 6H, H_3CNP), 7.54, 7.68 (2d, J_{H-H} = 7.8 Hz, 2 × 1H, 5- and 8-HAr), 8.07-8.31 (m, 2 × 1H, 6- and 7-HAr), 8.61(d, $^4J_{P-H}$ =2.8 Hz, 1H, 4-CH), 9.82 (s.br, 1H, HN); ^{13}C-NMR ($CDCl_3$): δ 192 (d, $^1J_{P-C}$ = 136 Hz, C=O), 150.6 (d, $^2J_{P-C}$ = 13.6 Hz, 2-CAr), 133.7 (d, $^3J_{P-C}$ = 6.8 Hz, 4-CAr), 110.5 (d,$^2J_{P-C}$= 136 Hz, 3-CAr), 156.7, 134.2, 133.6, 131.5, 124.4, 122.7, (9-, 7-, 5-, 8-, 6-, 10-CAr), 37.5 (d, $^2J_{P-C}$ = 30.8 Hz, 6H, $PNCH_3$); ^{31}P-NMR ($CDCl_3$): δ 14.8 ppm; EI-MS: *m/z* (%): 262 [M^++1] (18), 217 (37), 174 (55), 137 (100). Anal. calcd for $C_{12}H_{12}N_3O_2P$ (261.2): C, 55.18; H, 4.63; N, 16.09; P, 11.86. Found: C, 55.23; H, 4.59; N, 16.05; P, 11.81.

*2-(Dimethylamino)-6-methyl-1,2-dihydro-3H-[1,2]azaphospholo [5,4-b]quinoline-3-one 2-oxide (**12b**).* This compound was obtained as yellow crystals, 937 mg (85%); mp 162–164°C (MeCN); IR: ν_{max} NH 3424, C=O 1726, P—O 1256, PNMe 1328, 835 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, H_3C-6Ar), 2.85 (d, $^3J_{P-H}$ = 11.6 Hz, 6H, H_3CNP), 7.27, 7.54 (2d, J_{H-H} = 6.5 Hz, 2 × 1H, 7-, 8-CH), 7.58 (s, 1H, 5-HC), 8.63 (d, $^4J_{P-H}$ = 2.8 Hz, 1H, 4-HAr), 9.84 (s.br, 1H, HN); ^{13}C-NMR ($CDCl_3$): δ 190.2 (d, $^1J_{P-C}$ = 140 Hz, C=O), 150.7 (d, $^2J_{P-C}$ = 11.6 Hz, 2-CAr), 136.8 (d, $^3J_{P-C}$ = 9.6 Hz, 4-CAr), 110.5 (d, $^2J_{P-C}$ = 14.5 Hz, 3-CAr), 156.4, 132.4, 131.5, 130.7, 129.6, 123.8 (9-, 7-, 6-, 5-, 8-, 10-CAr), 37.8 (d, $^2J_{P-C}$ = 29.5 Hz, CH_3NP), 20.8 (CH_3-6Ar); ^{31}P-NMR ($CDCl_3$): δ 14.2 ppm; EI-MS: *m/z* (%): 276 [M^++1](14), 231 (22), 203 (52), 156 (100). Anal. calcd for $C_{13}H_{14}N_3O_2P$ (275.2): C, 56.73; H, 5.13; N, 15.27; P, 11.25. Found: C, 56.78; H, 5.07; N, 15.19; P, 11.15.

The reaction of 1a,b with tetraethyl methylenebisphosophonate (13). Preparation of compounds 14a and 14b. To a stirred solution of 1.49 mL of the bisphosphonate (**13**, 5.2 mmol) and 10 mmol of Na in 10 mL EtOH was added dropwise to a solution of 4 mmol of the azide (**1a**, 0.79 g or **1b**, 0.85 g) in 15 mL EtOH at 0°C. The resulting mixture was allowed to warm to r.t. under stirred for ≈6 h (TLC). HCl (1*N*) was added (at –5°C) until the pH of the reaction mixture became acidic, followed by extraction with AcOEt (3mL × 50 mL), and the combined organic phase was dried over anh. Na_2SO_4. After removal of the solvent, under vacuum, the resulting residue was washed several times with light petroleum (40–60°C), and crystallized from the proper solvent to give **14a** or **14b**, respectively.

*(Z)-Diethyl (1-(diethoxyphosphino)-2-(tetrazolo[1,5-a]quinolin-4-yl)vinyl)phosphonate (**14a**).* This compound was obtained as orange crystals, 1.38 g (74%); mp 250–252°C ($CHCl_3$); IR: ν_{max} C=C, ylide 1618, P—O, free 1254, tetrazole 1180, P—O—C 1030 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.22, 1.34 (2dt, J_{H-H} = 6.6, $^4J_{P-H}$ = 4.8 Hz, 12H, $[H_3C.COP]_2$), 4.14 (2dq, J_{H-H} = 6.6, $^3J_{P-H}$ = 5.6 Hz, 8H, H_2COP), 5.55 (t, $^3J_{P-H}$ = 10.5 Hz, 1H, HC = CP_2), 7.78–7.85 (m, 2 × 1H, 9- and 10-HAr), 8.65 (s, 1H, 7-HAr), 8.72, 8.86 (2d, 2 × 1H, 8-, 11-HAr); ^{13}C-NMR (DMSO-d_6): δ 143.6 (d, $^4J_{P-C}$ = 4.5 Hz, 5-CAr), 133.8 (d, $^4J_{P-C}$ = 2.7 Hz, 7-CAr), 133.1 (d, $^2J_{P-C}$ = 22 Hz, *C*H=C, ylide), 128.8 (d, $^1J_{P-C}$ = 129.2 Hz, P-C=), 114.5 (d, $^3J_{P-C}$ = 7.2 Hz, 6-CAr), 138.1, 134.8, 133.1, 131.1, 127.9, 123.9 (12-, 8-, 11-, 9-, 10-, 13-CAr), 61.8 (d, $^2J_{P-C}$ = 9.8 Hz, CH_2OP), 16.3 (d, $^3J_{P-C}$ = 4.6 Hz, *C*H_3C.OP); ^{31}P-NMR (DMSO-d_6): δ 18.4 ppm; EI-MS: *m/z* (%): 469 [M^++1] (16), 440 (11), 426 (32), 289 (62),152 (100). Anal. calcd for $C_{19}H_{26}N_4O_6P_2$ (468.4): C, 48.72; H, 5.60; N, 11.96; P, 13.23. Found: C, 48.78; H, 5.55; N, 11.89; P, 13.16.

*(Z)-Diethyl (1-(diethoxyphosphino)-2-(9-methyltetrazolo[1,5-a] quinolin-4-yl)vinyl)-phosphonate (**14b**).* This compound was obtained as yellow crystals, 1.39 g (72%); mp 201–202°C (CH_2Cl_2) cm^{-1}; IR: ν_{max} C=C, ylide 1614, P—O, free 1248, tetrazole 1174, P—O—C 1082 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28, 1.33 (2dt, J_{H-H} = 6.8, $^4J_{P-H}$ = 3.9 Hz, 12H, $[H_3C.COP]_2$), 2.64 (s, 3H, H_3C-9Ar), 3.88, 4.26 (2dq, J_{H-H} = 6.8, $^4J_{P-H}$ = 6.5 Hz, 8H, H_2COP), 5.88 (t, $^3J_{P-H}$ = 10.5 Hz, 1H, HC=CP_2), 7.89, 8.03 (2m, 3 × 1H, 7-, 10- and 11-HAr), 8.43 (s, 8-HAr); ^{13}C-NMR (DMSO-d_6): δ 143.7 (d, $^4J_{P-C}$ = 4.5 Hz, 5-CAr), 135.4 (d, $^4J_{P-C}$ = 4.8 Hz, 7-CAr), 133.3 (d, $^2J_{P-C}$ = 28 Hz, *C*H=C, ylide), 129.6 (d, $^1J_{P-C}$ = 129.2 Hz, P—C=), 114.5 (d, $^3J_{P-C}$ = 7.2 Hz, 6-C), 140.06, 136.1, 132.0, 126.8, 126.4, 116.7 (12-, 9-, 10-, 8-, 13-, 11-CAr), 62.8 (d, $^2J_{P-C}$ = 9.8 Hz, CH_2OP), 20.4 (CH_3-9Ar), 16.1 (d, $^3J_{P-C}$ = 4.6 Hz, *C*H_3COP); ^{31}P-NMR (DMSO-d_6): δ 22.6 ppm; EI-MS: *m/z* (%): 483 [M^++1] (12), 454 (18), 440 (15), 426 (48), 289 (67), 152 (100). Anal. calcd for $C_{20}H_{28}N_4O_6P_2$ (482.4): C, 49.79; H, 5.85; N, 11.61; P, 12.84. Found: C, 49.85; H, 5.79; N, 11.59; P, 12.91.

Anti-inflammatory activity experiments *in vivo*; carrageenin-induced edema. ***Materials and Methods.*** *Animals.* All experiments have been conducted on adult Wistar strain albino rats of either sex, weighing between 150 and 200 g. Animals were kept in colony cages under identical housing conditions at an ambient temperature of 25°C ± 2°C and 45–55% relative humidity with 12 h light–dark cycle in the departmental animal room and fed on standard diet. Animals were acclimatized for a weak before use.

Experimental model of inflammation. Carrageenin-induced paw edema was used throughout the investigation.

*Standard drug Indomethacin (**A**), substrates (**1a, 1b**), and synthesized compounds (**5a–f, 6a–f, 12a,b, 14a,b**) and solutions.* (a) Powder of the pure carrageenin was used and fresh suspension was prepared in distilled water to make 1% carrageenin solution; (b) fresh tested compound solutions were made by adding 10 mg of the compound in 500 mg carboxymethyl cellulose and 50 mL distilled water.

Experimental Inflammation. It was produced by the following method: carrageenin-induced paw edema in rats: 1% carrageenin suspension was prepared as a homogeneous solution in distilled water. A volume of 0.1 mL of carrageenin solution was injected through a 26-gauge needle into the plantar surface of the left hind paw below the plantar aponeurosis. The volume of the paw was measured before and at different intervals for 4 h after injection of carrageenin. The difference in the paw volume before and after administration of the phlogistic agent was taken as the measure of pedal edema. The compounds whose effects have been studied on this particular model were administered as per schedule; (c) measurement of paw volume: the volume of hind paw of the rats up to the ankle joint was measured by plathysmographically by the mercury displacement method. The ankle joint of the rats was marked with a skin marking pencil and the paw was dipped in the mercury, so that the mark on the paw coincides with a prefixed line kept constant on the syringe. The level of the mercury was every time brought to the level of this line by adjusting the height of the displaced mercury. The difference in the paw volume before and after injection of the phlogistic agents was taken as a measure of pedal edema. The change in paw volume was expressed in "mL" of mercury displaced.

The anti-inflammatory activity was expressed as percentage inhibition of edema volume in the treated animals in comparison with the control group.

$$\% \text{ Inhibition of edema } = \frac{(V_c - V_t)}{V_c} \times 100$$

where V_c and V_t are the volumes of edema for the control and tested substance-treated animal groups, respectively, while potency of the tested compounds was calculated regarding Indomethacin, reference standard, treated group according to the following equation:

$$\%\text{Potency} = \frac{\%\,\text{Edema inhibition of tested compound treated group}}{\%\,\text{Edema inhibition of indomethacin treated group}} \times 100$$

Toxicity of the evaluated promised substituted quinoline heterocycles phosphor esters. The LD_{50} determination of the most promising synthesized anti-inflammatory active agents (**12a** and **14a**) was determined by the standard known LD_{50} method in mice. Albino mice weighing 20–25 g were divided into six groups of eight mice each. Administrations of the tested compounds (**12a** and **14a**) dissolved in the same vehicle solution in 500, 750, and 1000 mg/kg (body weight) were given intraperitoneally. The control groups were given in buffer solution only. The toxic symptoms, mortality rates, and postmortem findings in each group were recorded 24 h postadministration.

LD_{50} of the tested compounds were calculated according to the following formula:

$$LD_{50} = D_m - \sum(z \times d)/n$$

where D_m is the largest dose which kill all animals, z is the mean of dead animals between two successive groups, d is the constant factor between two successive doses, n is the number of animals in each group, Σ is the sum of $(z \times d)$.

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