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Note

Michael adducts – Synthons for a new class of 1,4-dispirocyclohexane derivatives

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A new class of 1,4-dispirocyclohexane derivatives have been prepared from 2,6-diaroyl-3,5-diarylcyclohexane-1,1,4,4-tetracarboxylic acid tetramethyl ester.

Keywords: Michael Addition, dimethyl malonate, dispiro cyclohexanes.

IPC: **Int.Cl.**[7] **C 07 C**

The chemistry of spiro-pyrimidines having barbituric acid moiety has drawn much attention in recent times due to their broad spectrum of chemotherapeutic properties such as hypnotic, antitumor, antiviral, anticonvulsant and analgesic[1]. A number of pyrazole and isoxazole derivatives also possess bacteriostatic, antidiabetic, analgesic, antiarrhythmic, anti-inflammatory, antifungal and antiviral properties[2]. Earlier spiro-pyrimidinetriones and pyrazolidinediones were obtained by the condensation of cycloalkane-1,1-dicarboxylic acids or esters with urea[1a,3] and hydrazine hydrate[3,4]. However, the latter preparation involves multistep processes and vigorous reaction conditions. On the other hand, spiro-pyrimidinetriones were prepared by the reaction of α,β-unsaturated compounds with barbituric acid and its derivatives[5]. However, there are no reports on the synthesis of dispiro-pyrimidinetriones, -pyrazolidinediones and -isoxazolidinediones with heterocyclic rings in a spiro arrangement with respect to carbocyclic ring. In the present study, the reactive intermediate dimethyl 2,2-bis (1-benzoyl-2-phenyl-vinyl) malonate **1**, which has *gem*-diester and 1,4-diene functionalities was employed to synthesise the target molecules. The compound **1** is obtained by the Knoevenagel reaction of 1,5-diaryl-3,3-dimethoxycarbonyl-1,5-pentanedione with araldehydes under PTC conditions[6]. In fact, the latter is used as a versatile intermediate for various heterocycles such as substituted dihydropyridines, pyrans, thiopyrans, spiro-pyrimidinetriones, pyrazolidinediones and isoxazolidine-diones[6,7].

Results and Discussion

The present communication deals with the double Michael addition of the active methylene compound, dimethyl malonate to **1,** which is a source of 1,4-dispirocyclohexane derivatives. The addition of dimethyl malonate to **1** in the presence of sodium methoxide in methanol resulted in 2,6-diaroyl-3,5-diarylcyclohexane-1,1,4,4-tetracarboxylic acid tetramethyl ester **2** (75-85%). The ^{1}H NMR spectrum of **2a** showed two doublets for methine protons (C-2 and C-6, and C-3 and C-5) at δ_H 4.65 and 4.53. The *J* values of 9.0 Hz indeed correspond to a dihedral angle close to 180^o which fits with a *trans* arrangement of substituents in a rigid chair conformation. Thus, it is evident that the bulkier groups present at C-2, C-3, C-5 and C-6 occupy equatorial positions in the preferred rigid conformation[8] (**Figure 1**). Cyclocondensation of **2** with urea, N,N′-dimethyl urea and thiourea in the presence of sodium methoxide in methanol afforded 7,16-diaroyl-8,15-diaryl-2,4,11,13-tetraazadispiro[5.2.5.2]hexadecane-1,3,5,10,12,14-hexaone **3**, 7,16-diaroyl-2,4,11,13-tetramethyl-8,15-diaryl-2,4,11,13-tetraazadispiro[5.2.5.2]hexadecane-1,3,5,10,12,14-hexaone **4** and 7,16-diaroyl-8,15-diaryl-3,12-dithioxo-2,4,11,13-tetraazadispiro[5.2.5.2]

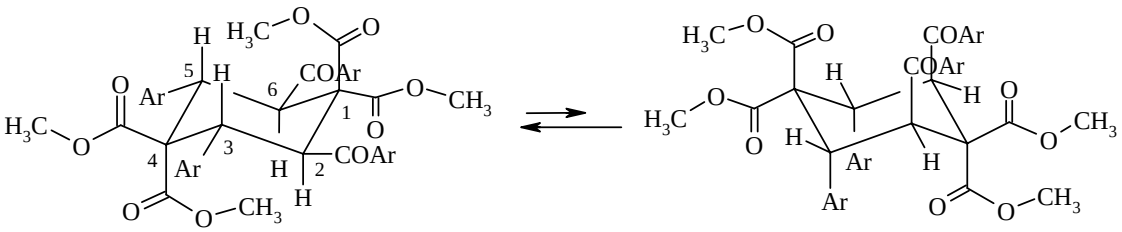
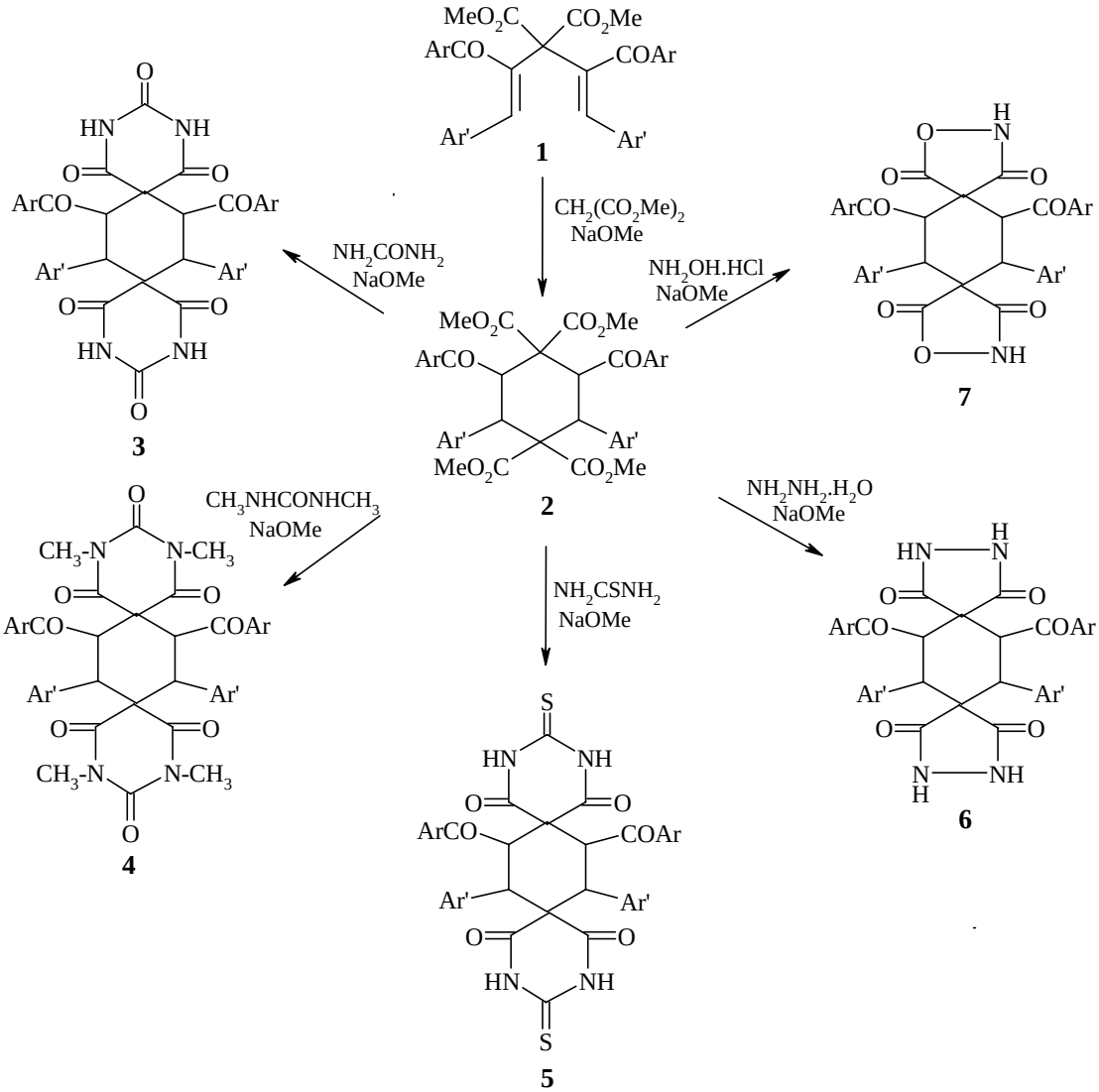


Figure 1

hexadecane-1,5,10,14-tetraone **5**. Similar nucleophilic reaction of **2** with hydrazine hydrate and hydroxylamine hydrochloride gave 6,14-diaroyl-7,13-diaryl-2,3,10,11-tetraazadispiro[4.2.4.2]tetradecane -1,4,9,12-tetraone **6** and 6,14-diaroyl-7,13-diaryl-2,10-dioxa-3,11-diazadispiro[4.2.4.2] tetradecane-1,4,9,12-tetraone **7** (**Scheme I** and **Table I**). The ^{1}H NMR spectra of compounds **3-5** showed two doublets at δ_H 3.69-3.73 and δ_H 3.79-3.85 for methine protons at C-8 and C-15, and C-7 and C-16. However, the compounds **6** and **7** displayed doublets at δ_H 3.68-3.89 and δ_H 3.78-4.09 for protons at C-7 and C-13, and C-6 and C-14. The coupling constant (J ~ 9.0 Hz) indicates that they possess *trans* geometry. Besides compounds **3** and **5-7** showed a broad singlet at δ_H 9.12-10.04 for NH proton which disappeared on deuteration. The absence of signals corresponding to carbomethoxy groups supports the evidence for formation of products. Thus, it is assumed that the nearly planar pyrimidinetrione/thioxopyrimidinedione/pyrazolidinedione/isoxazolidinedione units are situated perpendicular to the average plane of the cyclohexane system (**Figure 2**). In ^{13}C NMR spectra of **3-7** the δ_C values around 20 and 40 were assigned



	Ar	Ar'
a	Ph	Ph
b	Ph	4-OMe.Ph
c	4-Cl.Ph	Ph

Scheme I

Table I — Physical data of compounds **1-7**

Compd	m.p. °C	Yield (%)	Mol. formula (Mol. wt.)	Found % (Calcd) C	H	N
1a	172-74	65	-	-	-	-
1b	190-92	63	-	-	-	-
1c	197-99	66	-	-	-	-
2a	235-37	75	$C_{40}H_{36}O_{10}$ (676.71)	71.12 (70.99	5.34 5.36	- -)
2b	202-04	78	$C_{42}H_{40}O_{10}$ (676.71)	68.54 (68.47	5.52 5.47	- -)
2c	218-20	85	$C_{40}H_{34}Cl_2O_{10}$ (745.60)	64.34 (64.44	4.64 4.60	- -)
3a	280-82	72	$C_{38}H_{28}N_4O_8$ (668.65)	68.34 (68.26	4.18 4.22	8.43 8.38)
3b	276-78	76	$C_{40}H_{32}N_4O_{10}$ (728.70)	66.04 (65.93	4.41 4.43	7.77 7.69)
3c	260-62	80	$C_{38}H_{26}Cl_2N_4O_8$ (737.54)	61.95 (61.88	3.39 3.35	7.52 7.60)
4a	286-88	70	$C_{42}H_{36}N_4O_8$ (724.76)	69.49 (69.60	5.06 5.01	7.81 7.73)
4b	274-76	74	$C_{44}H_{40}N_4O_{10}$ (784.81)	67.40 (67.34	5.17 5.14	7.22 7.14)
4c	254-56	79	$C_{42}H_{34}Cl_2N_4O_8$ (793.65)	63.63 (63.56	4.35 4.32	7.00 7.06)
5a	290-92	69	$C_{38}H_{28}N_4O_6S_2$ (700.78)	65.22 (65.13	4.00 4.03	8.12 7.99)
5b	295-97	75	$C_{40}H_{32}N_4O_8S_2$ (760.84)	63.20 (63.14	4.28 4.24	7.45 7.36)
5c	286-88	72	$C_{38}H_{26}Cl_2N_4O_6S_2$ (769.67)	59.25 (59.30	3.38 3.40	7.20 7.28)
6a	275-76	68	$C_{36}H_{28}N_4O_6$ (612.63)	70.70 (70.58	4.59 4.61	9.30 9.15)
6b	282-84	70	$C_{38}H_{32}N_4O_8$ (672.68)	67.77 (67.85	4.85 4.79	8.39 8.33)
6c	268-70	77	$C_{36}H_{26}Cl_2N_4O_6$ (681.52)	63.31 (63.44	3.90 3.85	8.30 8.22)
7a	256-58	73	$C_{36}H_{26}N_2O_8$ (614.60)	70.41 (70.35	4.30 4.26	4.61 4.56)
7b	265-66	70	$C_{38}H_{30}N_2O_{10}$ (674.65)	67.56 (67.65	4.45 4.48	4.08 4.15)
7c	246-48	76	$C_{36}H_{24}Cl_2N_2O_8$ (683.49)	63.35 (63.26	3.56 3.54	4.16 4.10)

to the methine carbons at C-8 and C-15, and C-7 and C-16 in **3-5** as well as at C-7 and C-13, and C-6 and C-14 in **6** and **7**. The δ_C values observed at 41-61 and at 51-76 were attributed to the tertiary carbons. The ^{13}C chemical shift values around 180 and 200 were due to the carbonyl carbons of substituted pyrimidinetrione/thioxopyrimidinedione, pyrazolidinedione, isoxazolidinedione and aroyl moieties. The IR spectra of **3-7** showed absorption bands in the region 1680-1695 cm^{-1} for ArCO. Apart from this, the compounds **3** and **5-7** exhibited bands at 3215-3310 for NH and 1654-1680 cm^{-1} for CONH. The compound **7** showed bands around 1750-1765 cm^{-1} for CO-O while **5** showed bands around 1254-1275 cm^{-1} for C=S.

In conclusion, a new class of hitherto unknown 1,4-dispirocyclohexane derivatives were prepared by exploiting the reactivity of *gem*-diester functionality in 2,6-diaroyl-3,5-diarylcyclohexane-1,1,4,4-tetracarboxylic acid tetramethyl ester with different nucleophiles.

Experimental Section

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 3:1). The IR spectra were recorded on a Perkin Elmer–337 IR spectrometer in KBr pellets. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The elemental analyses were performed at Punjab University, Chandigarh, India. The compound **1** was prepared according to the literature procedure[6].

General procedure for the preparation of 2,6-diaroyl-3,5-diarylcyclohexane-1,1,4,4-tetracarboxylic acid tetramethyl ester 2. The compound **2** (0.005 mole) was dissolved in MeOH (10 mL) and to this dimethyl malonate (0.007 mole) was added and stirred well. To this 10% NaOMe (5 mL) was added slowly and stirring was continued for 4-5 hr. The separated solid was filtered, washed with ice-cold alcohol, dried and purified by recrystallisation from methanol.

Compound 2a: ^1H NMR: δ 3.82 (s, 12H, CO_2CH_3), 4.53 (d, 2H, C_3 and C_5-H, J = 9.4 Hz), 4.65 (d, 2H, C_2 and C_6-H, J = 9.4 Hz), 7.06-7.86 (m, 20H, Ar-H); ^{13}C NMR: δ 22.1 (C-3 and C-5), 38.6 (C-2 and C-6), 43.1(C-1), 52.7 (CO_2CH_3), 58.9 (C-4), 176.0 (CO_2CH_3), 200.7 (COAr).

Compound 2b: ^1H NMR: δ 3.65 (s, 6H, Ar-OCH_3), 3.85 (s, 12H, CO_2CH_3), 4.55 (d, 2H, C_3 and C_5-H, J = 9.8 Hz), 4.62 (d, 2H, C_2 and C_6-H, J = 9.8 Hz), 7.14-7.92 (m, 18H, Ar-H); ^{13}C NMR: δ 22.4 (C-3 and C-5), 39.4 (C-2 and C-6), 42.8(C-1), 52.1 (CO_2CH_3), 58.4 (C-4), 176.2 (CO_2CH_3), 200.5 (COAr).

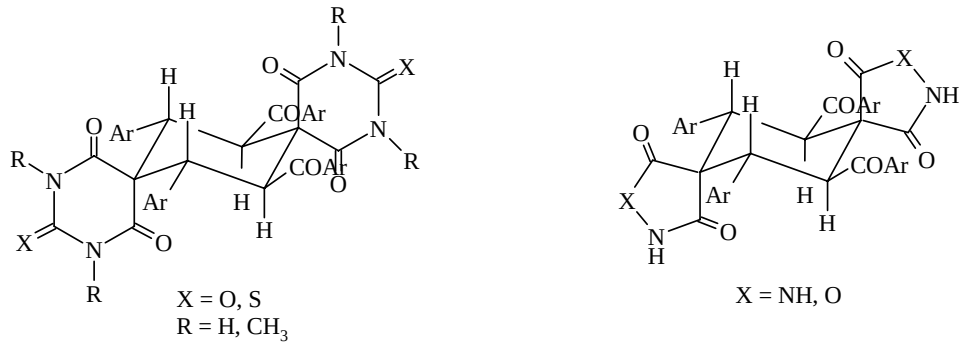


Figure 2

Compound 2c: ^{1}H NMR: δ 3.70 (s, 12H, CO_2CH_3), 4.56 (d, 2H, C_3 and C_5-H, *J* = 9.7 Hz), 4.61 (d, 2H, C_2 and C_6-H, *J* = 9.7 Hz), 7.16-7.83 (m, 18H, Ar-H); ^{13}C NMR: δ 22.2 (C-3 and C-5), 39.8 (C-2 and C-6), 43.5 (C-1), 52.6 (CO_2CH_3), 57.8 (C-4), 175.9 (CO_2CH_3), 200.8 (COAr).

General procedure for the preparation of 7,16-diaroyl-8,15-diaryl-2,4,11,13-tetraazadispiro[5.2.5.2]-hexadecane-1,3,5,10,12,14-hexaone 3. A mixture of **2** (0.01 mole), urea (0.015 mole), MeOH (20 mL) and 10% NaOMe (5 mL) was refluxed for 4-6 hr. The solution was cooled and poured onto crushed ice containing HCl. The solid obtained was filtered, dried and purified by recrystallization from methanol.

Compound 3a: ^{1}H NMR: δ 3.73 (d, 2H, C_8 and C_{15}-H, *J* = 9.2 Hz), 3.80 (d, 2H, C_7 and C_{16}-H, *J* = 9.2 Hz), 7.08-7.89 (m, 20H, Ar-H), 9.24 (bs, 4H, NH); ^{13}C NMR: δ 22.3 (C-8 and C-15), 39.6 (C-7 and C-16), 46.2 (C-6), 61.4 (C-9), 178.9 (C-1, C-5, C-10 and C-14), 157.8 (C-3 and C-12), 200.5 (COAr).

Compound 3b: ^{1}H NMR: δ 3.64 (s, 6H, Ar-OCH_3), 3.71 (d, 2H, C_8 and C_{15}-H, *J* = 9.1 Hz), 3.85 (d, 2H, C_7 and C_{16}-H, *J* = 9.1 Hz), 7.02-7.85 (m, 18H, Ar-H), 9.20 (bs, 4H, NH); ^{13}C NMR: δ 21.4 (C-8 and C-15), 39.2 (C-7 and C-16), 45.8 (C-6), 51.7 (Ar-OCH_3), 60.4 (C-9), 177.7 (C-1, C-5, C-10 and C-14), 157.7 (C-3 and C-12), 201.5 (COAr).

Compound 3c: ^{1}H NMR: δ 3.72 (d, 2H, C_8 and C_{15}-H, *J* = 9.4 Hz), 3.82 (d, 2H, C_7 and C_{16}-H, *J* = 9.4 Hz), 7.11-7.86 (m, 18H, Ar-H), 9.22 (bs, 4H, NH); ^{13}C NMR: δ 22.6 (C-8 and C-15), 39.8 (C-7 and C-16), 46.6 (C-6), 61.6 (C-9), 178.6 (C-1, C-5, C-10 and C-14), 156.9 (C-3 and C-12), 202.3 (COAr).

General procedure for the preparation of 7,16-diaroyl-2,4,11,13-tetramethyl-8,15-diaryl-2,4,11,13-tetraazadispiro[5.2.5.2]hexadecane-1,3,5,10,12,14-hexaone 4. An equimolar mixture (0.01 mole) of **2** and N,N′-dimethyl urea, 10 % NaOMe (5 mL) in dry MeOH (20 mL) was refluxed for 9-12 hr. Then, it was cooled and poured onto crushed ice containing conc. HCl. The separated solid was collected by filtration, dried and purified by recrystallization from methanol.

Compound 4a: ^{1}H NMR: δ 2.70 (s, 6H,N-CH_3), 3.70 (d, 2H, C_8 and C_{15}-H, *J* = 9.1 Hz), 3.80 (d, 2H, C_7 and C_{16}-H, *J* = 9.1 Hz), 7.10-7.93 (m, 20H, Ar-H); ^{13}C NMR: δ 22.7 (C-8 and C-15), 28.5 (N-CH_3), 40.4 (C-7 and C-16), 41.5 (C-6), 56.8 (C-9), 176.8 (C-1, C-5, C-10 and C-14), 156.6 (C-3 and C-12), 199.8 (COAr).

Compound 4b: ^{1}H NMR: δ 2.74 (s, 6H,N-CH_3), 3.62 (s, 6H, Ar-OCH_3), 3.71 (d, 2H, C_8 and C_{15}-H, *J* = 9.3 Hz), 3.84 (d, 2H, C_7 and C_{16}-H, *J* = 9.3 Hz), 7.01-7.88 (m, 18H, Ar-H); ^{13}C NMR: δ 21.7 (C-8 and C-15), 28.6 (N-CH_3), 40.3 (C-7 and C-16), 41.7 (C-6), 55.9 (Ar-OCH_3), 51.9 (C-9), 176.2 (C-1, C-5, C-10 and C-14), 156.3 (C-3 and C-12), 200.9 (COAr).

Compound 4c: ^{1}H NMR: δ 2.72 (s, 6H,N-CH_3), 3.73 (d, 2H, C_8 and C_{15}-H, *J* = 9.2 Hz), 3.83 (d, 2H, C_7 and C_{16}-H, *J* = 9.2 Hz), 7.12-7.84 (m, 18H, Ar-H); ^{13}C NMR: δ 22.8 (C-8 and C-15), 29.3 (N-CH_3), 41.2 (C-7 and C-16), 42.6 (C-6), 56.3 (C-9), 177.1 (C-1, C-5, C-10 and C-14), 156.0 (C-3 and C-12), 201.5 (COAr).

General procedure for the preparation of 7,16-diaroyl-8,15-diaryl-3,12-dithioxo-2,4,11,13-tetraa-zadispiro [5.2.5.2]hexadecane-1,5,10,14-tetraone 5. A mixture of **2** (0.01 mole), thiourea (0.01 mole), MeOH (20 mL) and 10% NaOMe (5 mL) was refluxed for 11-12 hr. The solution was cooled and poured onto crushed ice containing HCl. The solid obtained was filtered, dried and purified by recrystallization from methanol.

Compound 5a: ^{1}H NMR: δ 3.69 (d, 2H, C_8 and C_{15}-H, *J* = 9.1 Hz), 3.82 (d, 2H, C_7 and C_{16}-H, *J* = 9.1 Hz), 7.10-7.89 (m, 18H, Ar-H), 9.14 (bs, 4H, NH); ^{13}C NMR: δ 21.8 (C-8 and C-15), 39.1 (C-7 and C-16), 45.9 (C-6), 61.7 (C-9), 180.9 (C-1, C-5, C-10 and C-14), 183.0 (C-3 and C-12), 201.8 (COAr).

Compound 5b: ^{1}H NMR: δ 3.63 (s, 6H, Ar-OCH_3), 3.70 (d, 2H, C_8 and C_{15}-H, *J* = 9.5 Hz), 3.79 (d, 2H, C_7 and C_{16}-H, *J* = 9.5 Hz), 7.04-7.85 (m, 18H, Ar-H), 9.18 (bs, 4H, NH); ^{13}C NMR: δ 22.6 (C-8 and C-15), 39.6 (C-7 and C-16), 44.3 (C-6), 51.3 (Ar-OCH_3), 61.4 (C-9), 179.6 (C-1, C-5, C-10 & C-14), 183.9 (C-3 and C-12), 200.5 (COAr).

Compound 5c: ^{1}H NMR: δ 3.77 (d, 2H, C_8 and C_{15}-H, *J* = 9.5 Hz), 3.83 (d, 2H, C_7 and C_{16}-H, *J* = 9.5 Hz), 7.18-7.94 (m, 18H, Ar-H), 9.12 (bs, 4H, NH); ^{13}C NMR: δ 21.6 (C-8 & C-15), 38.7 (C-7 and C-16), 45.2 (C-6), 60.5 (C-9), 180.1 (C-1, C-5, C-10 and C-14), 182.6 (C-3 and C-12), 200.4 (COAr).

General procedure for the preparation of 6,14-diaroyl-7,13-diaryl-2,3,10,11-tetraazadispiro[4.2.4.2]-tetradecane-1,4,9,12-tetraone 6. To a solution of 2 (0.01 mole) in MeOH (20 mL), 80% hydrazine hydrate (0.015 mmole), and 10% NaOMe (5 mL) were added and refluxed for 4-6 hr. The contents were cooled and poured onto crushed ice containing HCl. The separated solid was filtered, dried and purified by recrystallization from 2-propanol.

Compound 6a: ^{1}H NMR: δ 3.68 (d, 2H, C_7 and C_{13}-H, *J* = 9.3 Hz), 3.78 (d, 2H, C_6 and C_{14}-H, *J* = 9.3 Hz), 7.02-7.86 (m, 20H, Ar-H), 9.24 (bs, 4H, NH); ^{13}C NMR: δ 21.4 (C-7 and C-13), 38.5 (C-6 and C-14), 60.8 (C-5), 76.4 (C-8), 176.9 (C-1, C-4, C-9 and C-12), 198.6 (COAr).

Compound 6b: ^{1}H NMR: δ 3.62 (s, 6H, Ar-OCH_3), 3.71 (d, 2H, C_7 and C_{13}-H, *J* = 9.2 Hz), 3.82 (d, 2H, C_6 and C_{14}-H, *J* = 9.2 Hz), 7.08-7.85 (m, 18H, Ar-H), 9.22 (bs, 4H, NH); ^{13}C NMR: δ 20.7 (C-7 and C-13), 38.4 (C-6 & C-14), 51.94 (Ar-OCH_3), 60.9 (C-5), 75.9 (C-8), 176.8 (C-1, C-4, C-9 and C-12), 199.4 (COAr).

Compound 6c: ^{1}H NMR: δ 3.73 (d, 2H, C_7 and C_{13}-H, *J* = 9.1 Hz), 3.85 (d, 2H, C_6 and C_{14}-H, *J* = 9.1 Hz), 7.15-7.69 (m, 18H, Ar-H), 9.26 (bs, 4H, NH); ^{13}C NMR: δ 20.3 (C-7 & C-13), 39.3 (C-6 and C-14), 61.2 (C-5), 76.8 (C-8), 177.2 (C-1, C-4, C-9 and C-12), 200.2 (COAr).

General procedure for the preparation of 6,14-diaroyl-7,13-diaryl-2,10-dioxa-3,11-diazadispiro-[4.2.4.2]tetradecane-1,4,9,12-tetraone 7. A mixture of 2 (0.01 mole), hydroxylamine hydrochloride (0.015 mole), MeOH (20 mL) and 10% NaOMe (5 mL) was refluxed for 5-6 hr. It was cooled and poured onto crushed ice containing HCl. The solid obtained was filtered, dried and purified by recrystallization from 2-propanol.

Compound 7a: ^{1}H NMR: δ 3.89 (d, 2H, C_7 and C_{13}-H, *J* = 9.2 Hz), 4.08 (d, 2H, C_6 and C_{14}-H, *J* = 9.2 Hz), 7.04-7.12 (m, 20H, Ar-H), 10.01(bs, 2H, NH); ^{13}C NMR: δ 21.4 (C-7 and C-13), 39.7 (C-6 and C-14), 52.4 (C-5), 68.5 (C-8), 173.4 (C-1, and C-9), 181.5 (C-4 & C-12), 198.6 (COAr).

Compound 7b: ^{1}H NMR: δ 3.61 (s, 6H, Ar-OCH_3), 3.78 (d, 2H, C_7 and C_{13}-H, *J* = 9.4 Hz), 4.04 (d, 2H, C_6 and C_{14}-H, *J* = 9.4 Hz), 6.98-7.79 (m, 18H, Ar-H), 9.98 (bs, 2H, NH); ^{13}C NMR: δ 21.9 (C-7 & C-13), 39.6 (C-6 and C-14), 52.6 (C-5), 51.72 (Ar-OCH_3), 68.3 (C-8), 173.6 (C-1, & C-9), 181.3 (C-4 and C-12), 199.9 (COAr).

Compound 7c: ^{1}H NMR: δ 3.85 (d, 2H, C_7 and C_{13}-H, *J* = 9.2 Hz), 4.09 (d, 2H, C_6 and C_{14}-H, *J* = 9.2 Hz), 7.12-7.93 (m, 18H, Ar-H), 10.04 (bs, 2H, NH); ^{13}C NMR: δ 21.8 (C-7 and C-13), 39.0 (C-6 and C-14), 51.9 (C-5), 69.0 (C-8), 173.8 (C-1, and C-9), 182.1 (C-4 and C-12), 198.7 (COAr).

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References

1 a) Voronin V G, Polevaya O Yu, Makhanova V G, Landau M A, Kolbanov V M, Privol'neva T P, Chugunov V V & Lavertskaya E F, *Khim-Farm Zh*, 10, **1976**, 43.
b) Aboul-Enein M N & El-Azzouny A A, *Acta Pharm Suec*, 23, **1986**,107.

2 a) Saharia G S & Sharma H R, *Indian J Pharm*, 37, **1975**, 47.
b) Heinemann H, Wolfgang K, Owe S, Gerd B & Ulrich K, *Ger Offen D E*, **1986**, 3424586; *Chem Abstr*, 105, **1986**, 42788e.
c) Varmini G L, Gluseppe D & Paolo G, *Mycopathol*, 58, **1976**, 39.
d) Gerald L G, Scriven F V E, James G K & Lowell M, *Eur Patent*, **1988**, 269308; *Chem Abstr*, 109, **1988**, 211058g.

3 Al-Asmawi M I, Ghoneim K M & Khalifa M, *Pharmazie*, 35, **1980**, 591.

4 a) Cairns H, Huntur W H & Lee T B, *Brit Patent*, **1967**, 1084267; *Chem Abstr*, 68, **1968**, 12970h.
b) Abdehmajid C & Houda F, *Ann Pharm Fr*, 38, **1980**, 429.

5 Otto H H & Triepel J, *Ann Chem*, **1976**, 1982.

6 Padmavathi V, Jagan Mohan Reddy B, Rajagopala Sarma M & Padmaja A, *Indian J Chem*, 43B, **2004**, 2459.

7 a) Padmavathi V, Balaiah A, Venugopal Reddy K, Padmaja A & Bhaskar Reddy D, *Indian J Chem*, 41B, **2002**, 1670.
b) Padmavathi V, Balaiah A & Bhaskar Reddy D, *J Heterocyclic Chem*, 39, **2002**, 649.
c) Padmavathi V, Balaiah A, Ramana Reddy T V, Jagan Mohan Reddy B & Bhaskar Reddy D, *Heteroatom Chem*, 14, **2003**, 513.

8 Bhaskar Reddy D, Padmavathi V & Muralidhar Reddy M, *Indian J Chem*, 31B, **1992**, 407 and references cited therein.