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Synthesis and Characterization of a Series of 1-Aryl-4-[Aryldiazenyl]-piperazines. Part II[1]. 1-Aryl-4-(2-Aryl-1-Diazenyl)-piperazines with Fluoro-, chloro-, Methyl-, Cyano- and Acetyl Substituents in The 1-Aryl Group

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Abstract: This paper reports the synthesis and characterization of eight series of 1-aryl-4-(2-aryl-1-diazenyl)-piperazines **(12 to 19)**. Several series of these triazenes have been synthesized by the diazotization of a primary arylamine followed by diazonium coupling with a secondary arylpiperazine . The arylpiperazines used in this study are: 1-phenylpiperazine, 1-(4-fluorophenyl-)piperazine, 1-(4-chlorophenyl-)piperazine, 1-(3,4-dichlorophenyl-)piperazine, 1-(2-methylphenyl-)-piperazine, 1-(4-acetophenyl-)-piperazine, 1-(2-pyridyl-)piperazine and 2-cyanophenylpiperazine. These new triazenes (series **12-19**) have been identified with a cocktail of contemporary spectroscopic techniques, notably infra-red and nuclear magnetic spectroscopy, supported by high resolution electron ionization mass spectrometry.

Keywords: 1-Arylpiperazine, Aryldiazenylpiperazines, Diazonium Coupling, IR spectroscopy, Mass Spectrometry, NMR, Triazene.

INTRODUCTION

The chemistry of triazenes has been explored since the latter part of the eighteenth century. Most of the work centered on the chemistry of the 1-aryl-3,3-dialkyltriazenes **(1)** and to a lesser extent on the chemistry of the monoalkyltriazenes **(2)**. The field of investigation of anti-tumour triazenes was established in the 1950s with the discovery of the biological activity of DTIC, also known as Dacarbazine, 5-(3,3-dimethyltriazen-1-yl)imidazole-4-carboxamide **(3)** [1] and in the 1980s with the discovery of temozolomide, also known as Temodal, (3,4-dihydro-3-methyl-4-oxoimidazo 5,1-d -*as*-tetrazine-8-carboxamide) **(4)** [2]. The mechanism of action of these drugs is only partially understood, but researchers do agree that the effectiveness of triazene-based antitumour agents may be due to their ability to alkylate DNA. These drugs are still considered very effective therapies, especially Dacarbazine in the treatment of malignant melanomas [3] and Temodal for brain cancers [4].

From an alternative perspective, the medicinal chemistry of piperazine derivatives has attracted considerable interest. Research on arylpiperazines **(5)** is quite extensive due to their biological applications. They are especially known for their high affinity toward serotonin receptors, chiefly 5-HT1A receptors. Many common anxiolytics (*antianxiety agents*) and antidepressants incorporate arylpiperazines [5]. It is believed that arylpiperazine derivatives act as 5-HT1A receptor antagonists [6]. The possibility of combining the structural unit of a triazene with that of a piperazine raises interesting questions regarding the biological activity that might be generated from such a combination.

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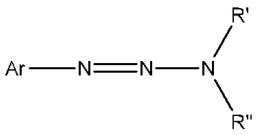
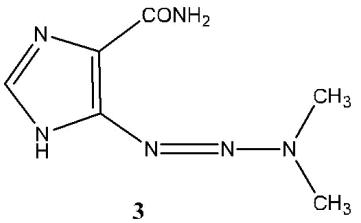
[1] For part I in this series please see the Open Org Chem J, 2015, 9, 35-42.



1 R', R" = alkyl

2 R' = H, R" = alkyl



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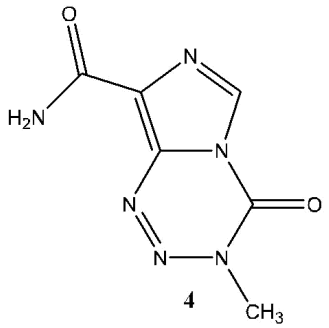

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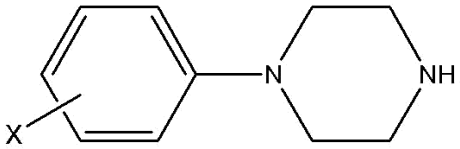

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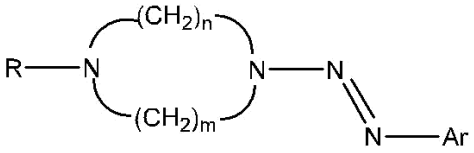

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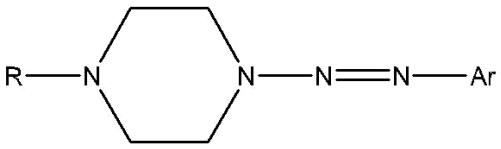
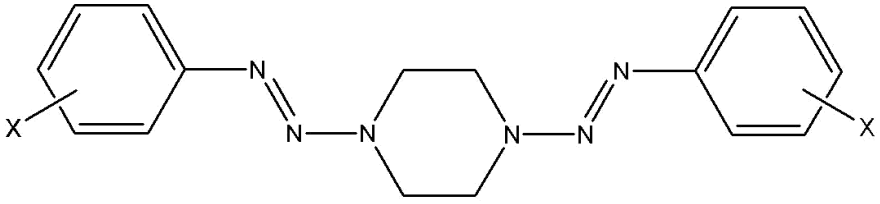


7a R = CH_3

b R = $CO_2C_2H_5$



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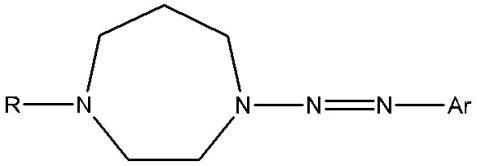
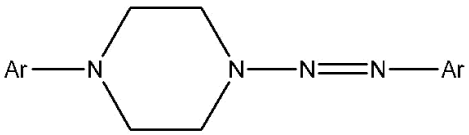


9 R = CH_3

10 R = ArN=N



11

Vaughan *et al*. recently explored and expanded the range of triazene derivatives of piperazines in a series of papers. The structures investigated use (1, x)-diazocycloalkanes **(6)** where m = 1 or 2 and n = 2, 3, 4, or 5, as the general structure. The specific structures varied the R moiety, the homology of the piperazine ring, or a combination of the two. In a previous report [7], the 1-(2-aryl-1-diazenyl-) 4-methylpiperazines **(7a)** were prepared by reaction of 1-methylpiperazine with the appropriate diazonium salt; this work also reported the analogous synthesis of the N-ethoxycarbonylpiperazines **(7b)**. A subsequent study [8] of the diazonium coupling reaction with piperazine itself in 2 : 1 proportions resulted in the isolation and identification of the bis-triazene series **(8)**. Some of the compounds in this series had been previously synthesized, but characterization had not been in depth [9].

A further paper in Vaughan's series [10] studied the effects of different piperazine ring homology, specifically diazepanes **(9 and 10)**. One possible direction for further study arising from these papers would involve the synthesis of a series of compounds maintaining the (1, *x*)-diazocycloalkane base structure **(6)** with the piperazine ring, while further adding to different functional groups on the R group. The R group has included alkylated and esterified substituents, as well as the aryldiazenyl group in *bis*-triazenes **(8 - 10)**. A logical next step would be to synthesize a series with the R group as an aryl moiety **(11)**. This extension will further add to the information on similar series, and provide a synthetic method for future studies. Additional interest in these new compounds is derived from the potential medicinal applications of compounds of type **11**.

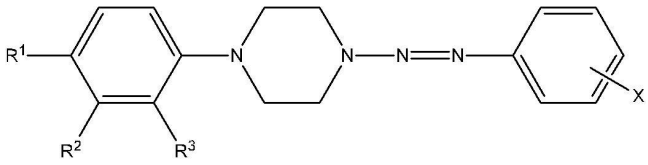
In this paper, several novel compounds of a new series of triazenes **(12-17)** have been synthesized and characterized.

The series has also been extended to the triazene series **(18 and 19)**.

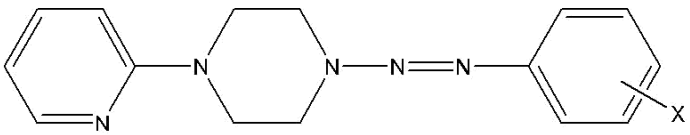
All compounds have been purified and characterized by IR and NMR spectroscopy and high resolution mass spectrometry (EI).

EXPERIMENTAL

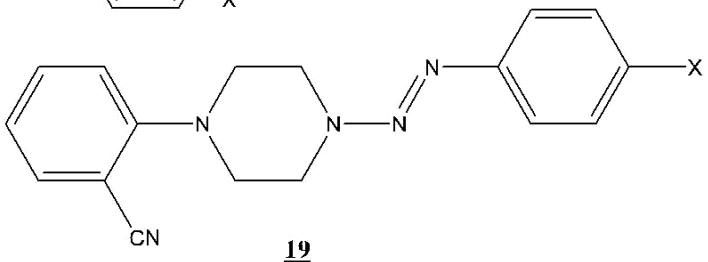
For details of the experimental methods such as IR, NMR, mass spectrometry, melting point measurement, *etc*., see any of the prior references of this author [7, 8, 10].



12 $R^1 = R^2 = R^3 = H$
13 $R^1 = F, R^2 = R^3 = H$
14 $R^1 = Cl, R^2 = R^3 = H$
15 $R^1 = R^2 = Cl, R^3 = H$
16 $R^1 = R^2 = H, R^3 = CH_3$
17 $R^1 = CH_3OC, R^2 = R^3 = H$



18



19

1-Aryl-4-(2-aryl-1-Diazenyl)-Piperazines (Series 12 to 19 Inclusive)

General Procedure

An aromatic primary amine (0.010 mol) was dissolved in 3M HCl (12.0 mL), and placed in an ice bath to cool to 0ºC. Sodium nitrite (0.011 mol), dissolved in water (3.0 mL) was added to the solution, and stirred for 0.5 hours. Concurrently, the appropriate aryl-piperazine (0.011 mol) was dissolved in water (1.0 mL), and cooled to 0ºC. If necessary to dissolve the alkylpiperazine, a small amount of 3M HCl (1.0 to 3.0 mL) was added. The piperazine solution was added slowly to the diazonium salt solution, and the resulting mixture was stirred for 0.5 hours. The solution was then neutralized with saturated sodium bicarbonate and left stirring in the cold for two hours. The product was collected using vacuum filtration if it was a solid and by extraction procedures if it was an oil. The solids were purified by recrystallization using an appropriate solvent. Oily products were isolated by extraction of the aqueous reaction mixture with dichloromethane, drying the organic layer over anhydrous magnesium sulphate, followed by evaporation of the solvent under vacuum.

RESULTS AND DISCUSSION

1-Aryl-4-(2-aryl-1-diazenyl)-piperazines: Synthesis

1-Aryl-4-(2-aryl-1-diazenyl)-piperazines (Series **12**-**17**) were produced in good to excellent yields (20 - 99%) by reaction of a diazonium salt with a specific N-arylpiperazine. Physical data and IR spectroscopic data of these compounds are listed in Tables **1**-**6**. The integrity of all compounds was verified by high-resolution mass spectrometry (EI) (see Tables **7**-**12**). { See structures in the Introduction section above.}

Table 1. Summary of physical and IR spectroscopic data of the 1-phenyl-4-(2-aryl-1-diazenyl)-piperazine series (12).

Series #	X	% Yield	M.P. (C)	Recr. Solv.	Crystal Appearance	IR (cm^{-1})	
12c	*p*-CH_3	39	164 - 166	Ethanol	Tiny pale Yellow needles	OOP	819
12d	*p*-Br	55	157 - 159	Ethanol	Tiny Orange needles	OOP	830
12e	*p*-OCH_3	20	182 - 184	Ethanol	lustrous metallic Plates	OOP C-O	834 1157, 1245
12f	*p*-$COCH_3$	51	165 - 167	Ethanol	Small Orange plates	OOP C=O	843 1681
12g	*p*-Cl	38	161 - 162	Ethanol	Lustrous gold Plates	OOP	834
12i	*o*-Br	95	Oil	Oil	-	OOP	760

Table 2. Summary of physical and IR spectroscopic data of the 1-(4-fluorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (13).

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal appearance	IR (cm^{-1})	
13a	*p*-CO_2CH_3	99	151.8 - 152.4	Ethanol	Orange Fibrous Needles	OOP C=O C-O	865 1710 1277
13b	*p*-Br	99	185.9 - 186.5	Ethanol	Tiny pale Yellow needles	OOP	837
13c	*p*-CH_3	72	171.9 - 172.8	Ethanol	Pale flesh-colored plates	OOP	814

Table 3. Summary of physical and IR spectroscopic data of the 1-(4-chlorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (14).

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR (cm^{-1})	
14a	*p*-CO_2CH_3	36	211.0 - 211.8	Ethanol	Orange-Yellow Needles	OOP C=O C-O	865 1704 1272
14b	*p*-CN	49	185.3 - 186.0	Ethanol	Gold needles	OOP C≡N	850 2218
14c	*p*-Br	93	226.8 - 227.8	Ethanol	Creamy yellow Needles	OOP	837
14d	*p*-CH_3	52	195.2 - 196.3	Ethanol	Pale pink Needles	OOP	816
14e	*p*-OCH_3	30	192.9 - 194.0	Ethanol	Pale pink Plates	OOP C-O	836 1028, 1240
14f	*p*-NO_2	89	218.5 - 221.4	Ethyl acetate	Lustrous Blood-red needles	OOP NO_2	863 1327, 1506

Table 4. Summary of physical and IR spectroscopic data of the 1-(3, 4-dichlorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (15).

Series #	X	% Crude	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR(cm^{-1})	
15a	*p*-CN	98	162 - 163	Ethanol	Fibrous Off-white Prisms	OOP C≡N	842 2223
15b	*p*-$CHOCH_3$	98	155 - 156	Ethanol	Lustrous reddish gold plates	OOP C=O	846 1675
15c	*p*-Br	55	146 - 147	Ethanol	Light brown needles	OOP	836
15d	*p*-OCH_3	34	131 - 133	Ethanol	Pale pink needles	OOP C-O	837 1034, 1245
15e	*p*-NO_2	53	150 - 151	Ethanol	Small lustrous red Needles	OOP NO_2	851 1339, 1595
15f	*p*-CH_3	36	130.3 - 130.9	Ethanol	Small pale pink Needles	OOP	823
15g	3-py	104	Oil	Oil	-	OOP	838
15h	*m*-CF_3	48	Oil	Oil	-	OOP	803

Table 5. Summary of physical and IR spectroscopic data of the 1-(ortho-tolyl)-4-(2-aryl-1-diazenyl)-piperazine series (16).

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR (cm-1)	
16a	*p*-NO2	46	143.0 - 144.1	Cyclohexane	Blood-red Needles	OOP NO2	855 1321, 1507
16b	*p*-Cl	60	104.9 - 105.5	Ethanol	Creamy yellow needles	OOP	846
16c	*p*-$CO_2C_2H_5$	62	105.5 - 106.1	Ethanol	Large orange needles	OOP C=O C-O	859 1711 1269
16d	*p*-$COCH_3$	53	115.1 - 115.9	Ethanol	Red-gold lustrous needles	OOP C=O	845 1675
16e	*p*-$CONH_2$	11	222.2 - 223.4	Ethanol	Orange prisms	OOP C=O N-H	857 1658 3289, 3328
16f	*p*-OCH_3	53	131.6 - 133.2	Cyclohexane	Dark red prisms	OOP C-O	833 1010, 1242
16g	H	61	Oil	Oil	-	OOP	813

Table 6. Summary of physical and IR spectroscopic data of the 1-(4-acetophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (17).

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR (cm^{-1})	
17a	*p*-CO_2CH_3	98	235.3 - 236.1	Ethanol	Yellow prisms	OOP C=O ester C=O ketone C-O ester	861 1706 1664 1280
17b	*p*-Br	93	231.6 - 232.4	Ethanol	Pale yellow prisms	OOP C=O ketone	837 1659
17c	*p*-CH_3	65	193.7 - 194.6	Ethanol	Lustrous pink plates	OOP C=O ketone	847 1674
17d	p-NO_2	90	217-218	Ethanol	Fine rusty-red needles	C═O ketone Nitro group OOP	1665 1513 & 1337 861
17e	*p*-CN	90	150-165	-	Amorphous brown clumps	C≡N C═O ketone OOP	2222 1658 843
17f	*p*-CO_2Et	93	177-178	Ethanol	Fine Lemon-yellow prisms	C═O ester C═O ketone C—O OOP	1705 1664 1282 859
17g	H	94	179-180	Ethanol	Fine pale yellow plates	C═O ketone OOP para OOP mono	1673 817 771

Table 7. Summary of mass spectroscopic data of the 1-phenyl-4-(2-aryl-1-diazenyl)-piperazine series (12).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
12c	*p*-CH_3	$C_{17}H_{20}N_4$	280.1688	280.1697
12d	*p*-Br	$C_{16}H_{17}N_4Br$	344.0636	344.0632
12e	*p*-OCH_3	$C_{17}H_{20}N_4O$	296.1637	296.1622
12f	*p*-$COCH_3$	$C_{18}H_{20}N_4O$	308.1637	308.1636
12g	*p*-Cl	$C_{16}H_{17}N_4Cl$	300.1142	300.1143
12i	*o*-Br	$C_{16}H_{17}N_4Br$	344.0636	344.0653

Table 8. Summary of mass spectroscopic data of the 1-(4-fluorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (13).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
13a	*p*-CO_2CH_3	$C_{18}H_{19}N_4O_2F$	342.1492	342.1487
13b	*p*-Br	$C_{16}H_{16}N_4FBr$	362.0542	362.0525
13c	*p*-CH_3	$C_{17}H_{19}N_4F$	298.1594	298.1603

Table 9. Summary of mass spectroscopic data of the 1-(4-chlorophenyl)-4-(2-aryl-1-diazenyl)-piperazin series (14).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
14a	*p*-CO_2CH_3	$C_{18}H_{19}N_4O_2Cl$	358.1196	358.1195
14b	*p*-CN	$C_{17}H_{16}N_5Cl$	325.1094	325.1101
14c	*p*-Br	$C_{16}H_{16}N_4ClBr$	378.0247	378.0248
14d	*p*-CH_3	$C_{17}H_{19}N_4Cl$	314.1298	314.1295
14e	*p*-OCH_3	$C_{17}H_{19}N_4OCl$	330.1247	330.1239
14f	*p*-NO_2	$C_{16}H_{16}N_5O_2Cl$	345.0992	345.1000

Table 10. Summary of mass spectroscopic data of the 1-(3, 4-dichlorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (15).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
15a	*p*-CN	$C_{17}H_{15}N_5C_{12}$	359.0704	359.0700
15b	*p*-$COCH_3$	$C_{18}H_{18}N_4OC_{12}$	376.0857	376.0846
15c	*p*-Br	$C_{16}H_{15}N_4C_{12}Br$	411.9857	411.9848
15d	*p*-OCH_3	$C_{17}H_{18}N_4OC_{12}$	364.0857	364.0821
15e	*p*-NO_2	$C_{16}H_{15}N_5O_2C_{12}$	379.0602	379.0613
15f	*p*-CH_3	$C_{17}H_{18}N_4C_{12}$	348.0908	348.0917
15g	3-py	$C_{15}H_{15}N_5C_{12}$	335.0704	335.0700
15h	*m*-CF_3	$C_{17}H_{15}N_4F_3C_{12}$	402.0626	402.0611

Table 11. Summary of mass spectroscopic data of the 1-(ortho-tolyl)-4-(2-aryl-1-diazenyl)-piperazine series (16).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
16a	*p*-NO_2	$C_{17}H_{19}N_5O_2$	325.1538	325.1548
16b	*p*-Cl	$C_{17}H_{19}N_4Cl$	314.1298	314.1298
16c	*p*-$CO_2C_2H_5$	$C_{20}H_{24}N_4O_2$	352.1899	352.1881
16d	*p*-$COCH_3$	$C_{19}H_{22}N_4O$	322.1793	322.1801
16e	*p*-$CONH_2$	$C_{18}H_{21}N_5O$	323.1746	323.1751
16f	*p*-OCH_3	$C_{18}H_{22}N_4O$	310.1793	310.1797
16g	H	$C_{17}H_{20}N_4$	280.1688	280.1689

The 1-(2-pyridyl)-4-(2-aryl-1-diazenyl-)piperazines (series **18**) were prepared by diazotization of the arylamine and coupling with 1-(2-pyridyl-)piperazine. The 1-(2-cyanophenyl)-4-(2-aryl-1-diazenyl-)piperazines (series **19**) were prepared by diazotization of the aryl amine and coupling with 1-(2-cyanophenyl-)piperazine. Physical data and infrared frequencies of the compounds of **18** and **19** are provided in Tables **13** and **15**. Mass spectrometric data on these compounds are given in Tables **14** and **16**.

Table 12. Summary of mass spectroscopic data of the 1-(4-acetophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (17).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
17a	*p*-CO_2CH_3	$C_{20}H_{22}N_4O_3$	366.1692	366.1682
17b	*p*-Br	$C_{18}H_{19}N_4OBr$	386.0742	386.0726
17c	*p*-CH_3	$C_{19}H_{22}N_4O$	322.1793	322.1801
17e	*p*-CN	$C_{19}H_{19}N_5ONa$	356.1482	356.1483
17f	*p*-CO_2Et	$C_{21}H_{24}N_4O_3Na$	403.1741	403.1726

Table 13. Summary of physical and IR spectroscopic data of the 1-(2-pyridyl)-4-(2-aryl-1-diazenyl)-piperazine series (18).

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR (cm^{-1})	
18a	*p*-NO_2	71	197.5 - 198.2	Ethanol	Tiny orange-red prisms	OOP NO_2	855 1333, 1504
18b	*p*-CN	69	150.2 - 151.1	Ethanol	Lustrous creamy-orange plates	OOP C≡N	835 2217
18c	3-py	79	Oil	Oil	Lustrous metallic needles	OOP	810
18d	*p*-CO_2CH_3	59	146.3 - 147.0	Ethanol	Yellow prisms	OOP C=O C-O	855 1710 1282
18e	*p*-$COCH_3$	61	166.4 - 166.8	Ethanol	Buff prisms	OOP C=O	850 1672
18f	*p*-CH_3	55	111.7 - 112.3	Ethanol	Off-white needles	OOP	844
18g	*o*-Br	74	Oil	Oil	-	OOP	756

(Table 13) contd.....

Series #	X	% Yield	M.P. (°C)	Recr. Solv.	Crystal Appearance	IR (cm^{-1})	
18h	H	51	99.4 - 100.4	Ethanol	Large lustrous pale brown plates	OOP	758

Table 14. Summary of mass spectroscopic data of the 1-(2-pyridyl)-4-(2-aryl-1-diazenyl)-piperazine series (18).

Series #	X	Formula	Calc. Mass (amu)	Found Mass (amu)
18a	*p*-NO_2	$C_{17}H_{19}N_5O_2$	312.1334	312.1339
18b	*p*-CN	$C_{16}H_{16}N_6$	292.1436	292.1431
18c	3-py	$C_{14}H_{16}N_6$	268.1436	268.1438
18d	*p*-CO_2CH_3	$C_{17}H_{19}N_5O_2$	325.1538	325.1538
18e	*p*-$COCH_3$	$C_{17}H_{19}N_5O$	309.1589	309.1600
18f	*p*-CH_3	$C_{16}H_{19}N_5$	281.1640	281.1629
18g	*o*-Br	$C_{15}H_{16}N_5Br$	345.0589	345.0588
18h	H	$C_{15}H_{17}N_5$	267.1484	267.1495

Table 15. Physical and IR Spectroscopic data of the 1-(2-cyanophenyl-)4-(2-aryl-1-diazenyl-)piperazine series (19).

Series #	KS#	X	% yield	m.p. °C	Recr. Solv.	Crystal appearance	IR $cm.^{-1}$	
19a	KS72	p-CO_2CH_3	87	130 - 131	Ethanol	Lustrous yellow needles	755 1714 2228	OOP C=O C≡N
19b	KS75	p-CH_2	91	107- 108	Cyclohexane	Chunky pink needles	769 822 2224	OOP OOP C≡N
19c	KS74	p-Br	96	104.9- 105.3	Ethanol	Off-white plates	755 2221	OOP C≡N
19d	KS76	p-OCH_3	36	130- 131	Ethanol	Metallic buff needles	765 828 1247 2218.5	OOP OOP C–O C≡N

Table 16. Mass spectroscopic data of the 1-(2-cyanophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (19).

Cpd	KS	Formula	Calc. mass (amu)	Found mass (amu)
19a	KS72	$C_{19}H_{19}N_5O_2$	349.1538	349.1534
19b	KS75	$C_{18}H_{19}N_5$	305.1640	305.1640
19c	KS74	$C_{17}H_{16}N_5Br$	369.0589	369.0585
19d	KS76	$C_{18}H_{19}N_5O$	321.1589	321.1580

Infrared Spectral Analysis

All compounds in series **12 - 19** were characterized by IR spectroscopy in order to confirm the presence of the appropriate aryl substituents and to confirm the expected substitution pattern of the aryl rings with reference to the OOP bending vibrations of aromatic-Hgroups C. All of the compounds in series **12** show out-of-plane (OOP) bending vibrations of the substituted benzene ring. The compounds of other series display analogous IR bands. Aliphatic and aromatic carbon-hydrogen stretches are not reported because the nujol peaks overwhelm the peaks of interest. In the case of the oil (**12i**), for which the IR spectrum was collected as a neat liquid, aliphatic carbon-hydrogen peaks were found at 2820 and 2976 cm^{-1}, and an aromatic carbon-hydrogen peak was found at 3064 cm^{-1}.

Significantly, it should be noted here that the analysis of the compounds of series **12** with the strongly electron-withdrawing substituent, p-nitro-, p-cyano- and p-methoxycarbonyl-, namely compounds **12h, 12a and 12b,** is not included in this paper. The reason for this omission is that the products of these reactions are not pure and we believe that the formation of these triazenes is accompanied by the formation of isomeric azo-compounds. The formation of

azo-compounds is only observed in the case of these three compounds. All other compounds of series **12** behave "*normally*" and afford single compounds characterized as the triazenes shown. Furthermore, the compounds of series **13 - 19** behave "*normally*" and do not give rise to isomeric azo compounds. The evidence that corroborates the azo compound hypothesis is somewhat involved, requiring the synthesis and characterization of model azo compounds. These results will be described in full detail in a follow-up paper to this one.

^{1}H NMR Spectral Analysis of Series 12 to 19

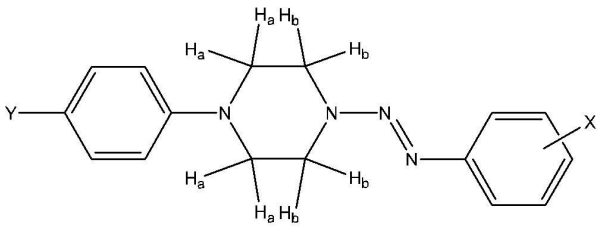
The proton nuclear magnetic resonance data of the members of series **12 to 19** is listed in Tables **17-24**. These results provided unequivocal structural information for the new triazenes of series **12 to 19**. Fig. (**1**) shows the labeling of the piperazine-ring protons described in the analysis information found in the Tables **17-24**. The aromatic resonance signals of the para-disubstituted compounds (**12c–g**) displayed the expected multiplicity of an AA'BB' system.

Table 17. Summary of ^{1}H NMR spectroscopic data of the 1-phenyl-4-(2-aryl-1-diazenyl)-piperazine series (12).

Series #	X	Aromatic (9H)		H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		Phenyl Ring	Aryl Ring				
12c	*p*-CH_3	6.92 (1H, t, J=6.2), 7.00 (2H, d, J=7.6) 7.30 (2H, t, J=7.9)	7.16 (2H, d, J=8.1), 7.37 (2H, d, J=8.2)	3.36 (t)	3.92 (t)	5.2	2.35 (3H, s)
12d	*p*-Br	6.92 (1H, t, J=7.3), 6.98(2H, d, J=7.9), 7.31 (2H, t, J=8.0)	7.34 (2H, d, J=8.8), 7.46 (2H, d, J=8.8)	3.36 (t)	3.95 (t)	5.3	---
12e	*p*-OCH_3	6.89 - 6.93 (1H, m), 6.99 (2H, d, J=8.1), 7.30 (2H, t, J=7.9)	6.90 (2H, d, J=8.9), 7.44 (2H, d, J=8.9)	3.60 (t)	3.89 (t)	5.2	3.82 (3H, s)
12f	*p*-$COCH_3$	6.84 (1H, t, J=7.3), 7.01 (2H, d, J=7.9), 7.26 (2H, t, J=7.9)	7.48 (2H, d, J=8.7), 7.97 (2H, d, J=8.7)	3.39 (br)	3.98 (t)	5.4	2.56 (3H, s)
12g	*p*-Cl	6.92 (1H, t, J=7.3), 6.98 (2H, d, J=7.8) 7.31 (2H, t, J=8.3)	7.28 - 7.32 (2H, m), 7.40 (2H, d, J=8.7)	3.36 (t)	3.95 (t)	5.3	---
12i	*o*-Br	6.93 (1H, t, J=7.1), 6.99 - 7.05 (2H, m), 7.26 - 7.32 (2H, m)	6.99 - 7.05 (1H, m), 7.26 - 7.32 (1H, m), 7.44 (1H, d, J=8.1), 7.60 (1H, d, J=7.5)	3.38 (t)	4.04 (t)	5.1	---

Table 18. Summary of 1H NMR spectroscopic data of the 1-(4-fluorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (13).

Series #	X	Aromatic (8H)		H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		4-F-Ph Ring	Aryl Ring				
13a	*p*-CO_2CH_3	6.96 - 7.04 (4H, m)	7.51 (2H, d, J=8.7), 8.05 (2H, d, J=8.7)	3.29 (t)	4.04 (t)	5.2	3.92 (3H, s)
13b	*p*-Br	7.01 - 7.04 (4H, m)	7.36 (2H, d, J=8.7), 7.48 (2H, d, J=8.8)	3.29 (t)	3.99 (br)	5.2	---
13c	*p*-CH_3	6.99 - 7.07 (4H, m)	7.29 (2H, d, J=7.8), 7.41 (2H, d, J=8.4)	3.30 (t)	3.96 (t)	5.2	2.39 (3H, s)



12 Y=H
13 Y=F
14 Y=Cl
17 Y=$COCH_3$

Fig. (1). Structure and substituents of 1-aryl-4-(2-aryl-1-diazenyl)-piperazines (**12, 13,14, and 17**)) with piperazine ring protons labeled.

The piperazine resonance signals **(12c - g and 12i)** displayed the expected multiplicity of an A_2B_2 system. The 4-fluorophenyl ring resonance signals **(13a - c)** displayed a complicated splitting pattern. The signals were consistent within the series, and were found as a multiplet in the range δ6.96 - 7.04. This complicated pattern is due to the NMR activity of fluorine. The protons of the tolyl methyl substituent **(13c)** had δ2 a.39 singlet. The signal full NMR at information for series **(13)** can be found in Table **18**.

Table 19. Summary of ^{1}H NMR spectroscopic data of the 1-(4-chlorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (14).

Series #	X	Aromatic (9H)		H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		4-Cl-Ph Ring	Aryl Ring				
14a	*p*-CO_2CH_3	6.94 (2H, d, J=8.9), 7.27 (2H, d, J=8.8)	7.51 (2H, d, J=8.4), 8.04 (2H, d, J=8.5)	3.36 (t)	4.05 (t)	5.3	3.93 (3H, s)
14b	*p*-CN	6.92 (2H, d, J=8.8), 7.27 (2H, d, J=9.0)	7.53 (2H, d, J=8.5), 7.64 (2H, d, J=8.7)	3.36 (br t)	4.05 (t)	5.1	---
14c	*p*-Br	6.96 (2H, d, J=8.9), 7.29 (2H, d, J=8.6)	7.37 (2H, d, J=8.7), 7.51 (2H, d, J=8.7)	3.37 (t)	4.00 (t)	5.3	---
14d	*p*-CH_3	6.91 (2H, d, J=9.0), 7.25 (2H, d, J=9.0)	7.18 (2H, d, J=8.1), 7.38 (2H, d, J=8.3)	3.33 (t)	3.92 (t)	5.4	2.37 (3H, s)
14e	*p*-OCH_3	6.89 - 6.92 (2H, m), 7.25 (2H, d, J=8.9)	6.89 - 6.92 (2H, m), 7.45 (2H, d, J=9.0)	3.33 (t)	3.89 (t)	5.3	3.83 (3H, s)
14f	*p*-NO_2	6.94 (2H, d, J=8.9), 7.28 (2H, d, J=8.9)	7.55 (2H, d, J=9.0), 8.23 (2H, d, J=9.2)	3.38 (br)	4.10 (t)	5.4	---

The ^{1}H NMR analysis information of the 1-(4-chlorophenyl)-4-(2-aryl-1-diazenyl)-piperazines **(14)** is shown in Table **19**. ^{1}H NMR spectral analysis of the 1-(3,4-dichlorophenyl)-4-(2-aryl-1-diazenyl)-piperazines **(series 15)** provided unequivocal structural information for these triazenes. The NMR analysis information can be found in Table **20**, and the proton labeling is shown in Fig. (**2**).

Table 20. Summary of ^{1}H NMR spectroscopic data of the 1-(3, 4-diclorophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (15).

Series #	X	Aromatic (7H)				H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		Aryl Ring (4H)	3,4-diCl-Ph Ring						
			H_e (1H)	H_d (1H)	H_c (1H)				
15a	*p*-CN	7.51 (2H, d, J=8.5), 7.62 (2H, d, J=8.6)	7.32 (d, J=8.8)	6.81 (dd, J=2.8, 8.9)	7.03 (d, J=2.7)	3.37 (t)	4.03 (t)	5.2	---
15b	*p*-$COCH_3$	7.52 (2H, d, J=5.1), 7.97 (2H, d, J=4.9)	7.32 (d, J=9.0)	6.80 (dd, J=2.9, 8.8)	7.02 (d, J=2.9)	3.37 (t)	4.02 (t)	5.4	2.60 (3H, s)
15c	*p*-Br	7.34 (2H, d, J=8.7), 7.47 (2H, d, J=8.7)	7.30 (d, J=8.8)	6.79 (dd, J=2.9, 8.8)	7.01 (d, J=2.9)	3.35 (t)	3.93 (t)	5.3	---
15d	*p*-OCH_3	6.90 (2H, d, J=6.8), 7.44 (2H, d, J=8.9)	7.30(d, J=8.8)	6.78 (dd, J=2.9, 8.8)	6.78 (dd, J=2.9, 8.8)	3.33 (t)	3.87 (t)	5.4	3.82 (3H, s)
15e	*p*-NO_2	7.55 (2H, d, J=9.0), 8.23 (2H, d, J=9.0)	7.33 (d, J=8.9)	6.80 (dd, J=2.8, 8.9)	7.02 (d, J=2.9)	3.39 (br)	4.07 (t)	5.4	---
15f	*p*-CH_3	7.19 (2H, d, J=5.3), 7.38 (2H, d, J=8.4)	7.32 (d, J=8.9)	6.80 (dd, J=2.9, 8.8)	7.02 (d, J=2.9)	3.35 (t)	3.91 (t)	5.3	2.39 (3H, s)
15g	3-py	7.27 - 7.30 (1H, m), 7.76 (1H, dd, J=0.5, 8.2), 8.44 (1H, dd, J=0.5, 4.7), 8.72 (1H, d, J=2.3)	7.33 (d, J=8.9)	6.81 (dd, J=3.0, 8.9)	7.02 (d, J=2.9)	3.37 (t)	4.00 (t)	5.3	---
15h	m-CF_3	7.44 - 7.49 (2H, m), 7.64 (1H, d, J=7.2), 7.74 (1H, s)	7.33 (d, J=8.8)	6.81 (dd, J=2.9, 8.9)	7.03 (d, J=2.8)	3.37 (t)	4.00 (t)	5.3	---

The 3, 4-dichlorophenyl ring resonance signals **(15a – h)** displayed the general splitting pattern of a 1,3,4-trisubstituted aryl ring. Three hydrogen atoms, H_c, H_d, and H_e, were all identifiable (refer to Fig. **2**). Proton assignments were based on multiplicity and coupling constants. H_c was assigned its position because of its doublet and small coupling constant due to W-coupling with H_d. Its doublet signals resonate in the range δ7.30 – 7.33. H_d was assigned its position because of its doublet of doublets and two coupling constants. The small coupling constant matches H_c's, and

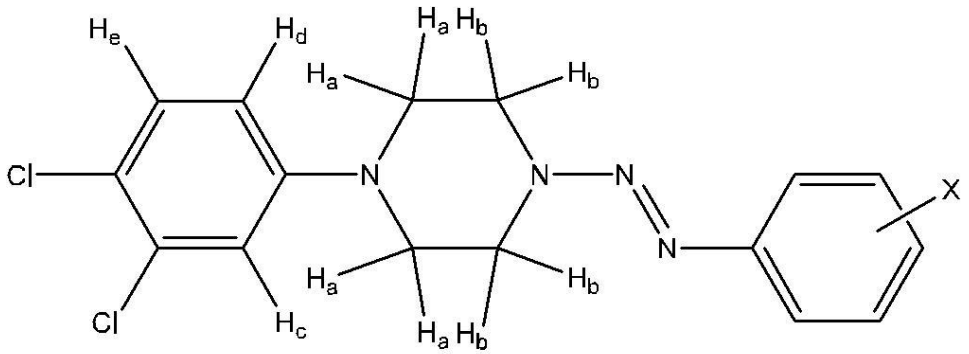
its large coupling constant corresponds to vicinal coupling with H_e. Its doublet of doublet signals resonates in the range δ 6.78 – 6.81. H_e was assigned its position because of its doublet and large coupling constant which matches H_d. Its doublet signals resonate between δ 7.01 – 7.03.

The piperazine resonance signals **(15a – h)** also displayed the expected multiplicity of an A_2B_2 system. The triplet signals were found between δ 3.33 – 4.07. The O-methyl group of the alkoxy substituent **(15d)** appears as a singlet atδ 3.82. The methyl protons that were part of the acetyl group **(15b)** appear as a singlet at δ 2.60. The tolyl methyl substituent **(15f)** had a singlet signal at δ 2.39.

Table 21. Summary of ^{1}H NMR spectroscopic data of the 1-(ortho-tolyl)-4-(2-aryl-1-diazenyl)-piperazine series (16).

Series #	X	Aromatic (8H)		CH_3 (3H)	H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		2-CH_3 Ring	Aryl Ring					
16a	*p*-NO_2	7.08 (2H, t, J=6.8), 7.21 (1H, d, J=7.6), 7.25 (1H, d, J=7.5)	7.56 (2H, d, J=9.2), 8.24 (2H, d, J=9.1)	2.41 (s)	3.14 (br)	4.11 (br)	---	---
16b	*p*-Cl	7.05 - 7.08(2H, m), 7.19-7.24(2H, m)	7.33 (2H, d, J=8.7), 7.42 (2H, d, J=8.7)	2.39 (s)	3.10 (t)	3.98 (t)	4.7	---
16c	*p*-$CO_2C_2H_5$	7.10 (2H, t, J=8.0), 7.21 (1H, d, J=7.6), 7.25 (1H, d, J=7.4)	7.52 (2H, d, J=8.7), 8.06 (2H, d, J=8.7)	2.43 (s)	3.16 (br)	4.11 (br)	---	1.41 (3H, t, J=7.1), 4.39 (2H, q, J=7.1)
16d	*p*-$COCH_3$	7.08 (2H, d, J=8.6), 7.21(1H, d, J=7.3), 7.25 (1H, d, J=7.3)	7.54 (2H, d, J=8.5), 7.98 (2H, d, J=8.4)	2.41 (s)	3.13 (br)	4.08 (br)	---	2.61 (3H, s)
16e	*p*-$CONH_2$	7.08 (2H, d, J=8.9), 7.21(1H, d, J=7.2), 7.24 (1H, d, J=7.5)	7.54 (2H, d, J=8.4), 7.83 (2H, d, J=8.4)	2.41 (s)	3.13 (br)	4.06 (br)	---	5.69 (1H, br), 6.03 (1H, br)
16f	*p*-OCH_3	6.91 (2H, d, 8.9), 7.20 (1H, d, J=7.3), 7.23 (1H, d, J=8.3)	7.04 - 7.06 (2H, m), 7.45 (2H, d, J=8.8)	2.37 (s)	3.08 (t)	3.90 (t)	5.1	3.84 (3H, s)
16g	H	6.90 (2H, d, J=7.9), 7.03 (1H, d, J=8.2), 7.10 (1H, d, J=7.2)	6.96 (1H, t, J=7.4), 7.23 (1H, t, J=7.6), 7.26 - 7.30 (3H, m)	2.40 (s)	3.18 (t)	4.46 (t)	5.2	---

Table **21** shows the details of the ^{1}H NMR analysis of the 1-(ortho-tolyl)-4-(2-aryl-1-diazenyl)-piperazines **16a-f**. The piperazine resonance signals **(16a - g)** displayed the multiplicity of an A_2B_2 system. The triplet signals were found between δ3.08 – 4.46. ^{1}H NMR spectral analysis of the 1-(4-Acetophenyl)-4-(2-aryl-1-diazenyl)-piperazines **(17 a-c)** (Fig. **1**) gave very similar results which are detailed in Table **22**.



15

Fig. (2). Structure and substituents of the 1-(3, 4-dichlorophenyl)-4-(2-aryl-1-diazenyl)-piperazines **(15)**.

Table 22. Summary of ^{1}H NMR spectroscopic data of the 1-(4-acetophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (17).

Series #	X	Aromatic (8H)		H_a (4H)	H_b (4H)	J_{ab} (Hz)	H_c (3H)	X
		4-$COCH_3$ Ph	Aryl Ring					
17a	*p*-CO_2CH_3	6.89 (2H, d, J=9.0), 7.89 (2H, d, J=9.0)	7.47 (2H, d, J=8.7), 8.01 (2H, d, J=8.7)	3.57 (t)	4.01 (t)	5.4	2.51 (s)	3.89 (3H, s)
17b	*p*-Br	6.92 (2H, d, J=9.0), 7.92 (2H, d, J=9.0)	7.35 (2H, d, J=8.8), 7.48 (2H, d, J=8.7)	3.58 (t)	3.98 (t)	5.4	2.55 (s)	---
17c	*p*-CH_3	6.93 (2H, d, J=9.0), 7.92 (2H, d, J=9.0)	7.18 (2H, d, J=8.1), 7.38 (2H, d, J=8.2)	3.57 (t)	3.94 (t)	5.5	2.54 (s)	2.36 (3H, s)
17d	*p*-NO_2	6.96(2H, d, J=9Hz) 7.96(2H, d, J=9Hz)	7.59(2H, d, J=7Hz) 8.26(2H,d ,J=7.1HZ	4.14 (t)	3.66 br (t)	5.5	2.59 (s)	-
17e	*p*-CN	6.90(2H,d J=9Hz) 7.91(2H,d, J=9Hz	7.50(2H,d, J=8.7Hz 7.62(2H,d, J=8.6Hz)	4.05 (t)	3.59 (t)	5.3	2.53 (s)	-
17f	*p*-CO_2Et	6.92(2H,d, J=9Hz) 7.91(2H,d, J=9.1Hz)	7.48(2H,d, J=8.8Hz) 8.04(2H,d, J=8.8 Hz	4.04 (t)	3.59 (t)	5.5	2.53 (s)	1.39(3H,t, J=7.2Hz 4.36(2H,q, J=7.5Hz
17g	H	6.91(2H,d, J=8.9Hz) 7.91(2H, d J=9.0Hz	7.20(1H,t J=7.3Hz) 7.36(2H,t, J=7.8Hz) 7.46(2H,dd J=5.8Hz)	3.96 (t)	3.57 (t)	5.4	2.53 (s)	-

^{1}H NMR analysis of the 1-(2-pyridyl)-4-(2-aryl-1-diazenyl)-piperazines **(18 a to h)** provided unequivocal structural information for these triazenes. The NMR analysis information can be found in Table **23**. ^{1}H NMR analysis of the 1-(2-cyanophenyl)-4-(2-aryl-1-diazenyl)-piperazines **(19 a to d)** provided unequivocal structural information for these triazenes. The NMR analysis information can be found in Table **24**.

Table 23. Summary of ^{1}H NMR spectroscopic data of the 1-(2-pyridyl)-4-(2-aryl-1-diazenyl)-piperazine series (18).

Series #	X	Aromatic (8H)		H_a (4H)	H_b (4H)	J_{ab} (Hz)	X
		2-Py Ring	Aryl Ring				
18a	*p*-NO_2	6.70 - 6.73 (2H, m), 7.53 - 7.57 (1H, m), 8.21 - 8.24 (1H, m)	7.54 (2H, d, J=9.0), 8.23 (2H, d, J=9.0)	3.83 (br t)	4.07 (t)	5.2	---
18b	*p*-CN	6.70 - 6.73 (2H, m), 7.53 (1H, d, J=8.6), 8.24 (1H, dd, J=1.1, 4.9)	7.52 (2H, d, J=8.6), 7.63 (2H, d, J=8.7)	3.82 (br t)	4.03 (t)	5.4	---
18c	3-py	6.68 - 6.69 (1H, m), 6.72 (1H, d, J=8.7), 7.52 - 7.55 (1H, m), 8.23 (1H, dd, J=1.2, 4.9)	7.27 - 7.29 (1H, m), 7.77 (1H, d, J=8.3), 8.42 (1H, dd, J=1.6, 4.8), 8.72 (1H, d, J=2.3)	3.80 (t)	3.99 (t)	5.4	---
18d	*p*-CO_2CH_3	6.69 - 6.70 (1H, m), 6.72 (1H, d, J=8.9), 7.53 - 7.56 (1H, m), 8.24 (1H, dd, J=1.1, 4.9)	7.51 (2H, dd, J=1.8, 8.7), 8.04 (2H, dd, J=1.8, 8.7)	3.81 (br t)	4.01 (t)	5.4	3.92 (3H, s)
18e	*p*-$COCH_3$	6.69 - 6.70 (1H, m), 6.72 (1H, d, J=8.6), 7.54 - 7.56 (1H, m), 8.24 (1H, dd, J=1.2, 4.9)	7.52 (2H, d, J=8.5), 7.97 (2H, d, J=8.7)	3.81 (br t)	4.02 (t)	5.3	2.60 (3H, s)
18f	*p*-CH_3	6.67 - 6.70 (1H, m), 6.72 (1H, d, J=8.6), 7.52 - 7.55 (1H, m), 8.24 (1H, dd, J=1.1, 5.0)	7.17 (2H, d, J=8.1), 7.39 (2H, d, J=8.4)	3.78 (br t)	3.91 (t)	5.4	2.36 (3H, s)
18g	*o*-Br	6.68 - 6.70 (1H, m), 6.72 (1H, d, J=8.6), 7.52 - 7.56 (1H, m), 8.24 (1H, dd, J=1.2, 4.9)	7.03 - 7.06 (1H, m), 7.26 - 7.29 (1H, m), 7.46 (1H, d, J=8.0), 7.61 (1H, d, J=7.9)	3.81 (br t)	4.02 (t)	5.4	---
18h	H	6.68 - 6.70 (1H, m), 6.72 (1H, d, J=8.5), 7.54 (1H, m), 8.24 (1H, dd, J=1.1, 4.7)	7.21 (1H, t, J=7.3), 7.37 (2H, t, J=7.9), 7.48 (2H, d, J=8.4)	3.79 (t)	3.95 (t)	5.4	---

Table 24. ^{1}H NMR spectroscopic data of the 1-(2-cyanophenyl)-4-(2-aryl-1-diazenyl)-piperazine series (19).

Series #	KS #	X	Piperazine Ha and Hb	Aryl-p Hc & Hd	Aryl-o He-Hh	X
19a	KS72	p-CO_2CH_3	3.55 4H, t 4.08 4H, t J=5.2Hz	8.02 2H, d 7.49 2H, d AA'BB'	7.05 2H, m 7.50 1H, m 7.60 1H, dd	3.90 3H, s
19b	KS75	p-CH_3	3.35 4H t 3.98 4H t J=5.15Hz	7.37 2H d 7.16 2H d AA'BB'	7.05 2H ddd 7.51 1H dt 7.60 1H dd	2.35 3H s
19c	KS74	p-Br	3.34 4H t 4.01 4H t J=5.2Hz	7.45 2H d 7.34 2H d AA'BB'	7.10 2H m 7.51 1H dt 7.61 1H dd	-
19d	KS76	p-OCH_3	3.35 4H t 3.95 4H t J=5.15Hz	6.89 2H d 7.43 2H d AA'BB'	7.05 2H m 7.51 1H dt 7.60 1H dd	3.82 3H s

CONCLUSION

Eight series of 1-aryl-4-(2-aryl-1-diazenyl)-piperazines were successfully synthesized: 1-phenyl-4-(2-aryl-1-diazenyl)-piperazines, 1-(4-fluorophenyl)-4-(2-aryl-1-diazenyl)-piperazines, 1-(4-chlorophenyl)-4-(2-aryl-1-diazenyl)-piperazines, 1-(3,4-dichlorophenyl)-4-(2-aryl-1-diazenyl)-piperazines, 1-(*ortho*-tolyl)-4-(2-aryl-1-diazenyl)-piperazines, 1-(4-acetophenyl)-4-(2-aryl-1-diazenyl)-piperazines, 1-(2-pyridyl)-4-(2-aryl-1-diazenyl)-piperazines and 1-(2-cyano phenyl)-4-(2-aryl-1-diazenyl)-piperazines. These compounds were identified by IR and ^{1}H NMR, and confirmed by high-resolution mass spectroscopy (EI).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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