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Synthesis of biologically active novel *bis* Schiff bases, *bis* hydrazone and *bis* guanidine derivatives

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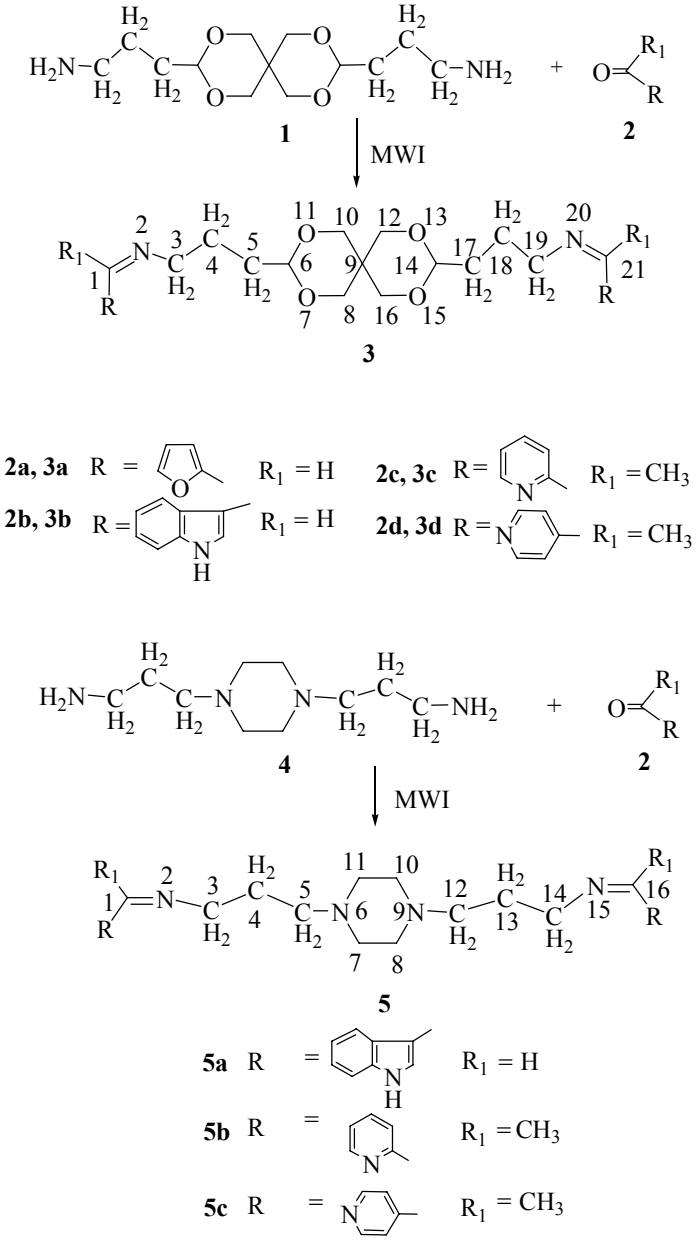
A number of *bis* Schiff's bases **3a-d** have been synthesized by condensation of 2,4,8,10 tetraoxaspiro[5,5]undecane 3,9-dipropanamine **1** with furfural, indole-3-aldehyde, 2-acetylpyridine, 4-acetylpyridine and **5a-c** by condensation of 1,4-*bis* (3-aminopropyl) piperazine **4** with indole-3-aldehyde, 2-acetylpyridine, 4-acetylpyridine, in high yields by using microwave irradiation. *Bis* hydrazone derivatives **8a-c** are obtained by condensation of 2,6-diacetylpyridine **7** with various arylsulfonylhydrazides using microwave irradiation. A number of bis guanidine derivatives **11a-j** are synthesized by condensation of 1,3-diaminoguanidine monohydrochloride **10** with various aldehydes **9a-c** and ketones **9d-j**. The structures assigned to these purified compounds i.e **3a-d, 5a-c, 8a-c**, and **11a-j**, are supported by correct spectral data and elemental analysis. Anti-inflammatory activities of **3b** and **11e** are comparable to standard drug phenyl butazone. Analgesic activities of **11e** and **3b** are compared with phenyl butazone and **3b** showed better activity then phenyl butazone.

Keywords: Schiff base, hydrazone, guanidine, anti-inflammatory, analgesic

Schiff bases, hydrazone and guanidine derivatives are important heterocyclic molecules. Schiff bases, hydrazone and guanidine derivatives possess various types of biological activities such as anti-inflammatory, analgesic[1,5], antimicrobial[6,7], antifungal[8,9], antitumor[10,11] and antimalarial[12,13] etc. Schiff bases are also employed as ligands for the complexation of metal ions[14]. Tempted by a variety of biological activities exhibited by Schiff bases, hydrazone and guanidine derivatives and in continuation of earlier efforts[15-17] in search of potent molecules exhibiting anti-inflammatory and analgesic activities a number of novel Schiff bases, hydrazone and guanidine derivatives have been synthesized.

Results and Discussion

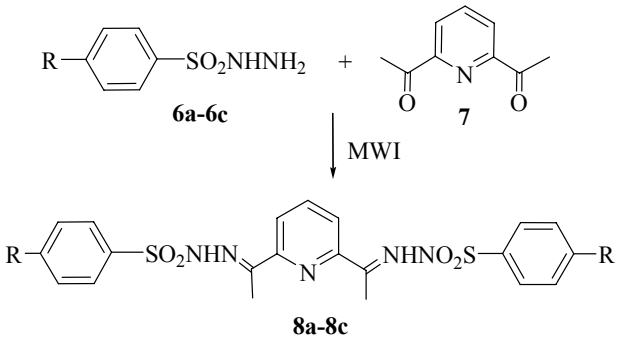
Furfural and 2,4,8,10 tetraoxaspiro[5,5]undecane 3,9-dipropanamine **1** (**Scheme I**) were mixed together in the molar ratio of 2:1. This mixture was subjected to microwave irradiation[18-20] at 300 Watt power, for 2 minutes. The crude product so obtained was washed with pet. ether and then recrystallized from methanol to give pure product (1-furan-2-yl-methylene)-[3-(9-{3-[(1-furan-2-ylmethylene)-amino]-propyl}-2,4,8,10-tetraoxa-spiro[5.5]undec-3-yl)-propyl]-amine **3a** (**Scheme I**) in 92% yield. Similarly condensation of 2,4,8,10 tetraoxaspiro[5,5] undecane 3,9-dipropanamine with indole-3-aldehyde, 2 acetyl pyridine and 4-acetylpyridine gave compounds **3b-d** (**Scheme I**) respectively. Spectral data of **3a-d** reported in experimental section of this paper fully support the structures assigned to them. Condensation of 1,4-bis(3-aminopropyl) piperazine **4** (**Scheme I**) with indole-3-aldehyde (in the molar ratio of 1:2) by using ethylacetate : methanol (4:1) as solvent of reaction and subjecting the reaction-mixture to microwave irradiation for seven minutes at 300 Watt power, after removal of the reaction solvent under reduced pressure a crude product **5a** was obtained. Compound **5a** was purified by crystallization from ethylacetate:methanol (1:1) to give pure product (1*H*-Indol-3-yl-methylene)-[3-(4-{3-[(1*H*-indol-3-yl-methylene)-amino]-propyl}pipera-zin-1-yl)propyl]-amine **5** (**Scheme I**) in 75% yield. Condensation of 1,4-bis (3-aminopropyl)piperazine with 2-acetyl pyridine and 4-acetyl pyridine gave products **5b** and **5c** (**Scheme I**) respectively. Spectral data of **5a, 5b** and **5c** reported in experimental section of this paper fully support the structures assigned to them. 2,6-diacetyl pyridine and phenyl sulfonyl hydrazide in the molar ratio of 1:2 were dissolved in ethylacetate : methanol (4:1) and then this reaction-mixture was subjected to



Scheme I — Synthesis of *bis* Schiff bases

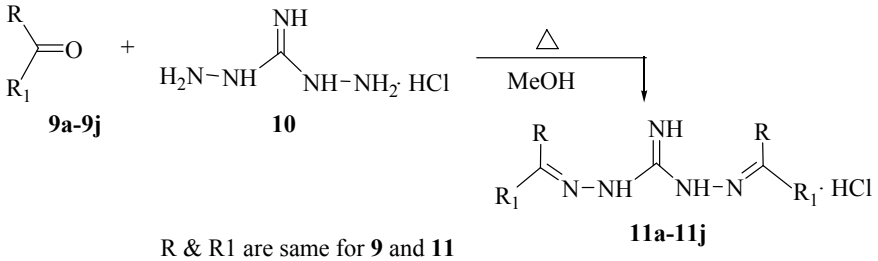
microwave irradiation for 10 minutes at 300 Watt power. Solvent was removed under reduced pressure and crude product so obtained was purified by crystallization from ethylacetate:methanol (1:1) to give pure product *N*′-(1-(6-(1-(phenylsulfonamido-imino)pyridine-2-yl)ethylidene) benzenesulfono-hydrazide **8a** (**Scheme II)** in 50% yield. Condensation of 2,6-diacetyl pyridine with 4-methyl benzene sulfonylhydrazide and 4-methoxy benzenesulfonyl hydrazide gave products **8b** and **8c** (**Scheme II**) respectively. Structures assigned to **8a, 8b** and **8c** are supported by spectral and analytical data reported in experimental section.

Condensation of furfural **9a** (**Scheme II**) with 1,3-diaminoguanidine monohydrochloride **10a** (**Scheme II**) in 2:1 molar ratio was carried out by heating under reflux in methanol for five hr. Solvent was removed under reduced pressure to give crude product **11a** which was purified by crystallization from methanol to give pure product **11a**, i.e. 1,3-*bis*-(furan-2-yl-

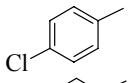
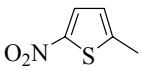
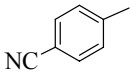
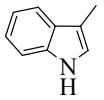
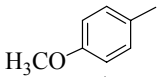


R is same for **6** and **8**

8a R = H, **8b** R = CH_3, **8c** R = OCH_3



R & R1 are same for **9** and **11**

	R	R_1		R	R_1
11a		H	**11f**		CH_3
11b		H	**11g**		CH_3
11c		H	**11h**		CH_3
11d	H_3C-CH_2	CH_3	**11i**		CH_3
11e		CH_3	**11j**		CH_3

Scheme II — Synthesis of *bis* hydrazone and *bis* guanidine derivatives

methylideneamino)guanidine hydrochloride in 89% yield. Similarly condensation of 5-nitro-2-thiophene carboxaldehyde **9b**, indole-3-carboxaldehyde **9c**, ethyl methyl ketone **9d**, acetophenone **9e**,4′-chloro-acetophenone **9f**, 4-acetyl benzonitrile **9g**, 4-methoxy-acetophenone **9h**, 3-acetylpyridine **9i**, and 4-acetyl-pyridine **9j** with diaminoguanidine hydrochloride **10** gave condensation products **11b-j** (**Scheme II**), respectively. Structures assigned to **11a-j** are fully supported by spectral and analytical data reported in experimental section.

Biological results

Compounds **3a-d, 5a-c**, **8a-c** and **11a-j** at 50 mg/kg p.o. were screened for anti-inflammatory activity in carrageenin induced[21] rat paw oedema model and results are summarized in **Table I**. Compounds **3a-d, 5a-c, 8a-c** and **11a-j** at 50 mg/kg p.o. exhibited 33, 46, 0, 0, 27, 26, 0, 12, 10, 6, 28, 19, 16, 20, 38, 22, 21, 25, 11 and 14% activity, respectively, whereas phenyl butazone exhibited 37% anti-inflammatory activity at 50 mg/kg p.o. Compounds **3b** and **11e** at 25 mg/kg p.o. showed 29 and 18%; and at 100 mg/ kg p.o. 62

Table I — Anti-inflammatory and analgesic activity of **3a-d, 5a-c, 8a-c** and **11a-j**

Compd tested	Dose mg/kg p.o.	Anti-inflam-matory activity (%)	Analgesic activity (%)
3a	50	33	50
3b	25	29	50
	50	46	70
	100	62	90
3c	50	0	25
	100	0	75
3d	50	0	0
5a	50	27	50
5b	50	26	40
5c	50	0	25
8a	50	12	25
8b	50	10	0
8c	50	6	0
11a	50	28	26
11b	50	19	14
11c	50	16	12
11d	50	20	14
11e	25	18	14
	50	38	34
	100	63	55
11f	50	22	19
11g	50	21	16
11h	50	25	22
11i	50	11	8
11j	50	14	12
Phenyl	25	17	13
butazone	50	37	33
	100	63	53

and 63% anti-inflammatory activity respectively, whereas phenylbutazone showed 17 and 63% anti-inflammatory activity at 25 mg/ kg po. and 100 mg/ kg p.o. respectively. Compounds **3b** and **11e** exhibited anti-inflammatory activity comparable to phenylbutazone.

Analgesic activity[22] evaluation of **3a-d**, **5a-c, 8a-c** and **11a-j** was carried out using acetic acid writhing assay and results are summarized in **Table I**. Compounds **3a-d**, **5a-c**, **8a-c** and **11a-j** at 50 mg/kg p.o. exhibited 50, 70, 25, 0, 50, 40, 25, 25, 0, 0, 26, 14, 12, 14, 34, 19, 16, 22, 8 and 12% analgesic activity respectively whereas phenylbutazone exhibited 33% analgesic activity. Compound **3b** exhibited 50% and 90% analgesic activity at 25 mg/kg p.o. and 100 mg/kg p.o. respectively whereas phenylbutazone exhibited 13% and 53% analgesic activity at 25 and 100 mg/kg p.o.

The indolyl Schiff base **3b** exhibited good anti-inflammatory and analgesic activity in comparison with the spiro Schiff bases having 2-pyridyl, 4-pyridyl or 2-furyl groups (**Table I)**, this may be due to the increase in the electron richness of the molecule. Similar situation is there in case of indolyl piperazine derivative **5a**, which exhibited better anti-inflammatory and analgesic activity as compared to 2-pyridyl or 4-pyridyl piperazine derivatives, this may again be due to the increase in the electron richness of the molecule. In case of guanidine derivatives indicate the presence of a phenyl substituted guanidine derivative i.e., **11e** exhibited better anti-inflammatory and analgesic activity than other guanidine derivatives, the reason could be that the molecule may be able to interact better with the target stereochemically.

Conclusion

A number of *bis* Schiff bases **3a-d, 5a-c**, *bis* hydrazone **8a-c** and *bis* guanidine derivatives **11a-j** have been synthesized and characterized by spectroscopic means. On screening for anti-inflammatory and analgesic activity compounds **3b** and **11e** exhibited good anti-inflammatory and analgesic activities.

Experimental Section

Melting points were determined on a JSGW apparatus and are uncorrected. Microwave oven model M197DL(SAMSUNG) was used for microwave irradiation. IR spectra were recorded using a Perkin-Elmer 1600FT spectrometer. ^{1}H NMR were recorded on a Bruker WH-300/Bruker av-500 spectrometer in. 5-15% (w/v) solution in appropriate deuterated solvent. FAB-MS was recorded on a Jeol SX-120 (FAB) spectrometer. GC-MS was recorded using Clarus 500 gas chromatograph from Perkin-Elmer built in MS detector was used. TLC was performed on silica gel G and spots were visualized by iodine vapours or by irradiation with UV light (254 nm). Elemental analysis was performed using a Vario EL III elementar analyzer.

General procedure for the synthesis of *bis* Schiff bases 3a-d

Synthesis of (1-furan-2yl methylene)-[3-(9-{3-[(1-furan-2-yl methylene)-amino]-propyl}-2,4,8,10-tetraoxa-spiro[5.5]undec-3-yl-propyl]-amine 3a

Furfural (0.192 g; 2 mmole) was taken in a beaker and to it was added 2,4,8,10-tetraoxa-spiro[5.5]-undecane 3,9-dipropanamine **1** (**Scheme I**) (0.274 g, 1

mmole), This reaction-mixture was subjected to microwave irradiation for 2 minutes at a power level of 300 Watt. The crude product so obtained was scratched with petroleum ether (5 mL) and then filtered and washed with petroleum ether to give solid product, which was further purified by crystallization from methanol to give pure product **3a.** Yield 0.395 g, 92%; m.p. 75ºC. FT-IR spectrum of **3a** show absorption band at 1648 cm^{-1} (due to C=N). While interpreting ^1H NMR of **3a** peak positions were assigned with the help of ^1H NMR of starting material i.e. **1**. ^1H NMR (300 MHz; DMSO-d_6 + D_2O): δ 1.63-1.69 (m, 4H, 2 × -CH_2-, C_4, C_{18}), 1.73-1.87 (m, 4H, 2 × -CH_2-, C_5, C_{17}), 3.30-3.34 (d, 2H, C_{12a} & C_{16a}), 3.49-3.60 (m, 8H, 4 × -CH_2- , C_3, C_{19}, C_8, C_{10}), 4.45-4.49 (t, 2H , 2 × CH, C_6, C_{14}), 4.51-4.57 (dd, 2H, C_{12b}, C_{16b}), 6.45-6.46 (q, 2H, Ar), 6.70-6.71(d, 2H, Ar), 7.492-7.496 (d, 2H, Ar), 8.06 (s, 2H, 2 × -CH=N-); GC-MS gave M^+ ion peak at *m/z* 430 (M^+, 5%); Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.18; H, 6.97; N, 6.51. Found: C, 64.19; H, 6.91; N, 6.21%.

(1*H*-Indol-3-ylmethylene)-[3-(9-{3-[(1*H*-indol-3-yl-methylene)-amino]-propyl}-2,4,8,10-tetraoxa-spiro [5.5] undec-3-yl)-propyl]-amine 3b.

Indole-3-aldehyde (0.290 g; 2 mmole) was taken in a conical flask and to it was added 2,4,8,10-tetraoxa-spiro [5.5]undecane3,9-dipropanamine (0.274 g, 1 mmole) and a mixture of ethylacetate:methanol (4:1/10 mL). The reaction contents were subjected to microwave irradiation for 4 minutes at power level of 600 Watt. After irradiation solvent was removed under reduced pressure and the residue so obtained was washed with diethyl ether to give crude product **3b**. Crude product **3b** so obtained was purified by crystallization from methanol to give pure product **3b**. Yield 0.359 g, 68%; m.p. 185ºC. IR (KBr): 3409 (-NH-) 1636 (C=N) and 1528 (Ar) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.72-1.78 (m, 8H, 4 × -CH_2-, C_4, C_{18}, C_5, C_{17}), 3.32-3.36 (d, 2H, C_{12a}, C_{16a}), 3.51-3.59 (m, 8H, 4 × -CH_2- , C_3, C_{19}, C_8, C_{10}), 4.47-4.54 (m, 4H, C_6, C_{14}, C_{12b}, C_{16b}), 7.10-7.16 (m, 4H, Ar), 7.39 -7.42 (d, 2H, Ar), 7.53 (s, 2H, Ar), 8.22-8.25 (d, 2H, Ar), 8.45 (s, 2H, 2 × -CH=N-); FAB-MS *m/z* 529 (MH^+,100%); Anal. Calcd. for $C_{31}H_{36}N_4O_4$: C, 71.24; H, 6.49; N, 10.38. Found: C, 70.90; H, 6.92; N, 10.81%.

Similarly compounds **3c-d** were synthesized**.**

(1-Pyridin-2-yl-ethylidene)-[3-{9-[3-(1-pyridin-2-yl-ethylideneamino)-propyl]-2,4,8,10-tetraoxa-spiro-[5.5]undec-3-yl-propyl]-amine 3c

Crystallized from MeOH; yield 57%; m.p. 185ºC; IR (KBr): 1633 (C=N) and 1575 (Ar) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.60-1.80 (m, 8H, 4 × -CH_2-, C_4, C_{18}, C_5, C_{17}), 2.30 (s, 6H, 2 × -CH_3), 3.30-3.38 (d, 2H, C_{12a}, C_{16a}), 3.40-3.52 (t, 4H, 2 ×-CH_2-, C_3C_{19}), 3.52-3.62 (m, 4H, 2 × -CH_2, C_8, C_{10}), 4.25-4.35 (dd, 2H, C_{12b}, C_{16b}), 4.50-4.62 (t, 2H, 2 × CH, C_6C_{14}), 7.40-7.45 (q, 2H, Ar), 7.78 -7.85 (m, 2H, Ar), 8.01-8.05 (d, 2H, Ar), 8.55-8.65 (d, 2H, Ar); FAB-MS *m/z* 481 (MH^+, 100%); Anal. Calcd. for $C_{27}H_{36}N_4O_4$: C, 67.50, H, 7.50, N, 11.66. Found: C, 67.80; H, 7.70; N, 11.51%.

(1-Pyridin-4-yl-ethylidene)-[3-{9-[3-(1-pyridin-4-yl-ethylideneamino)-propyl]-2,4, 8,10-tetraoxa-spiro-[5.5]undec-3-yl)-propyl]-amine 3d

Crystallized from MeOH; yield 70%; m.p. 110ºC; IR (KBr): 1629 (C=N) and 1590 (Ar) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$): δ 1.73-1.89 (m, 8H, 4 × -CH_2-, C_4, C_{18}, C_5, C_{17}), 2.21 (s, 6H, 2 × -CH_3), 3.34-3.36 (d, 2H, C_{12a}, C_{16a}), 3.46-3.67 (m, 8H, 4 × -CH_2-, C_3, C_{19}, C_8, C_{10}), 4.61-4.69 (m, 4H, C_6, C_{14}, C_{12b}, C_{16b}), 7.61-7.63 (q, 4H, Ar), 8.61-8.63 (q, 4H, Ar; FAB-MS *m/z* 481 (MH^+, 100%); Anal. Calcd. for $C_{27}H_{36}N_4O_4$: C, 67.50; H, 7.50; N, 11.66, S, Found: C, 67.40; H, 7.70; N, 11.51%.

General procedure for the synthesis of *bis* Schiff bases 5a-c

Synthesis of (1*H*-indol-3-ylmethylene)-[3-(4-{3-[(1*H*-indol-3-ylmethylene)-amino]-propyl}–piperazin-1-yl)-propyl]-amine 5a

1-4-*Bis*(3-aminopropyl) piperazine **4**. (0.200 g; 1 mmole) was taken in a conical flask and to it was added indole-3-aldehyde (0.290 g, 2 mmole), and ethylacetate: methanol (4:1) mixture (10 mL). The reaction contents were subjected to microwave irradiation for seven minutes at power level 300 Watt. After irradiation solvent was removed under reduced pressure and the residue left behind was washed with diethyl ether to give crude product **5a**, which was purified by crystallization from ethylacetate:methanol (1:1) to give pure product **5a**. Yield 0.340 g, 75%, m.p. 85ºC. FT IR of **5a** show absorption bands at 3412 (-NH-) cm^{-1}, 1637 (C=N), and 1530 (Ar), ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$): δ 1.86-1.95

(m, 4H, 2 × -CH_2- , C_4, C_{13}), 2.47-2.52 (m, 12H, 6 × -CH_2-, C_5, C_7, C_{11}, C_8, C_{10}, C_{12}), 3.59-3.63 (t, 4H, 2 × -CH_2-, C_3C_{14}), 7.13-7.28 (m, 5H, Ar), 7.39 -7.45 (m, 3H, Ar), 7.54 (s, 2H, 2 × –CH=N-), 8.23-8.26 (q, 2H, Ar), 8.47 (s, 2H, 2 × –NH-); FAB MS of **5a** gave MH^+ ion peak at *m/z* 455 (MH^+,100%). Anal. Calcd. for $C_{28}H_{34}N_6$: C, 74.00; H, 7.48; N, 18.50. Found: C, 73.90; H, 7.75; N,18.67%.

Similarly compounds **5b** and **5c** were synthesized.

(1-Pyridin-2-yl-ethylidene)-(3-{4-[(1-pyridin-2-yl-ethylideneamino)- methyl]pipera -zin-1-yl}-propyl)-amine 5b

Crystallized from MeOH; yield 82%; m.p. 75ºC; IR (KBr): 1632 (C=N) and 1571 (Ar) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 + $CDCl_3$): δ 1.92-2.01 (m, 4H, 2 × -CH_2-, C_4, C_{13}), 2.36 (s, 6H, 2 × -CH_3), 2.49-2.73 (m, 12H, 6 × -CH_2-, C_5, C_7, C_{11}, C_8, C_{10}, C_{12}), 3.54-3.58 (t, 4H, 2 × -CH_2-, C_3, C_{14}), 7.24-7.29 (q, 2H, Ar), 7.66 -7.72 (m, 2H, Ar), 8.05-8.07 (d, 2H, Ar), 8.53-8.59 (d, 2H, Ar; FAB-MS *m/z* 407 (MH^+, 100%); Anal. Calcd. for $C_{24}H_{34}N_6$: C, 70.93; H, 8.37; N, 20.68. Found: C, 70.53; H, 8.55; N, 20.12%.

(1-Pyridin-4-yl-ethylidene)- (3-{4-[(1-pyridin-4-yl-ethylideneamino) - methyl]piperazin-1-yl}-propyl)-amine 5c

Crystallized from ethyl Acetate; yield 79%; m.p. 60ºC; IR (KBr): 1635 (C=N) and 1595 (Ar) cm^{-1}, ^1H NMR (500 MHz, DMSO-d_6): δ 1.93-2.00 (q, 4H, 2 × -CH_2-, C_4, C_{13}), 2.23 (s, 6H, 2 × -CH_3), 2.36-2.52 (m, 12H, 6 × -CH_2-, C_5, C_7, C_{11}, C_8, C_{10}, C_{12}), 3.51-3.56 (t, 4H, 2 × -CH_2-, C_3, C_{14}), 7.61-7.63 (q, 4H, Ar), 8.61-8.63 (q, 4H, Ar); FAB-MS *m/z* 407.3 (MH^+, 100%); Anal. Calcd for $C_{24}H_{36}N_6$: C, 70.93; H, 8.37; N, 20.68. Found: C, 71.09; H, 8.03; N, 20.23%.

General procedure for the synthesis of hydrazone derivative 8a-c

Synthesis of *N′*-(1-(6-(1-(phenylsulfonamidoimino)-ethyl)pyridine-2- yl)ethylidene)benzenesulfonohydrazide 8a

2,6 Diacetyl pyridine **7** (0.163 g, 1 mmole) was taken in a conical flask and to it was added phenyl sulfonylhydrazide (0.344 g, 2 mmole) and ethyl-acetate: methanol (4:1) mixture (10 mL). The reaction contents were irradiated for 10 minutes at power level of 300 Watt. After the irradiation solvent was removed under reduced pressure and the residue left behind was washed with diethyl ether to give crude product **8a**. Crude product **8a** was purified by crystallization from ethylacetate: methanol (1:1) to give pure product **8a**. Yield 0.230 g, 49%; m.p. 190ºC; IR (KBr): 1621 (C=N) and 1575 (Ar) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + D_2O): δ 2.20 (s, 6H, 2 × –CH_3), 7.55 -7.62 (m, 6H, Ar), 7.70-7.80 (m, 3H, Ar), 7.90-8.00 (dd, 4H, Ar; ESI-MS *m/z* 472 (MH^+; 100 %); Anal. Calcd for $C_{21}H_{21}N_5S_2O_4$: C, 53.50; H, 4.45; N, 14.86; S, 13.58. Found: C, 53.80; H, 4.15; N, 14.65; S, 13.20%.

Similarly compounds **8b** and **8c** were synthesized.

4-Methyl-*N′*-(1-(6-(1-tosylamidoimino)ethyl)pyridine-2-yl)ethylidene)benzenesulfosulfonohydrazide 8b

Crystallized from MeOH; yield 50%; m.p. 180ºC; IR (KBr): 3481 (NH), 1633 (C=N), and 1573 (Ar) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + D_2O): δ 2.23 (s, 6H, 2 × -CH_3), 2.35 (s, 6H, 2 × -CH_3), 7.35-7.45 (d, 4H, Ar), 7.76-7.85 (m, 7H, Ar); GC-MS *m*/z 499 (M^+, 30%). Anal. Calcd for $C_{23}H_{25}N_5S_2O_4$: C, 55.31; H, 5.01; N, 14.02; S, 12.82. Found: C, 54.91; H, 4.67; N, 13.76; S, 12.65%.

4-Methoxy-*N′*-(1-(6-(1-((4-methoxyphenylsulfonamido)imino)ethyl)pyridine-2-yl)ethylidene)benzenesulfonohydrazide 8c

Crystallized from MeOH; yield 79%; m.p. 175ºC; IR (KBr): 3430 (NH), 1658 (C=N) and 1480 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 6H, 2 × -CH_3), 3.88 (s, 6H, 2 × -OCH_3), 7.18-7.19 (d, 4H, Ar), 7.82-7.83 (d, 2H, Ar), 7.86-7.87 (t, 1H, Ar), 7.92-7.94 (d, 4H, Ar), 10.77(s, 2H, exch, 2 × NH); GC-MS *m/z* 531(M^+, 13%); Anal. Calcd. for $C_{23}H_{25}N_5S_2O_6$: C, 51.97; H, 4.70; N, 13.18; S, 12.05. Found: C, 52.37; H, 4.41; N, 12.98; S, 12.42%.

General procedure for the synthesis of *bis* guanidine derivatives 11a-j

Synthesis of 1,3-*bis*-(furan-2-yl-methylidene-amino)guanidine hydrochloride 11a

Furfural (0.165 mL, 2 mmole) was added to a solution of 1.3-diaminoguanidine hydrochloride (0.125 g, 1 mmole) in methanol (10 mL), reaction-mixture was refluxed for 5 hr. Solvent was removed under reduced pressure to give an oily mass, this oily mass was triturated with diethylether to give crude product which was further purified by crystallization

from methanol to give pure product **11a**. Yield 89%; m.p. 80ºC; FT-IR of **11a** show absorption bands at 3351 and 3248 (-NH) 1641 (C=N) and 1473 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 6.63-6.64 (d, 2H, Ar); 7.06-7.07 (d, 2H, Ar), 7.83-7.84 (d, 2H, Ar), 8.22 (s, 2H, 2 × =CH-), 8.42 (bs, 2H, 2 × –NH, exch), 12.1 (bs, 2H, NH.HCl, exch); GC-MS of **11a** gave *m/z* 247 (MH^++1, 1.28%), 246 (MH^+, 12.42%), 245 ($M^{+\cdot}$, 100.00%); Anal. Calcd. for $C_{11}H_{12}N_5O_2Cl$: C, 46.89; H, 4.26; N, 24.86. Found: C, 46.63; H, 4.01; N,24.60%.

Similarly compounds **11b-j** were synthesized.

1,3-*Bis*-(5-nitrothiophene-2-yl-methylideneamino)-guanidine hydrochloride 11b

Crystallized from MeOH; yield 98%; m.p. 170ºC; IR (KBr): 3434 (-NH), 1623 (C=N), 1589, 1531 and 1499 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ: 7.67-7.68 (d, 2H, Ar), 8.15-8.16 (d, 2H, Ar), 8.60-8.63 (2s, 4H, 2 × =CH- + 2 × –NH, exch), 12.5 (bs, 2H, NH.HCl, exch). GC-MS: No M^+ ion peak observed but other peaks obtained i.e. *m/z* 155 ($C_5H_3N_2O_2S$, 0.92%); 128 ($C_4H_2NO_2S$, 0.91%)**.** Anal. Calcd. for $C_{11}H_{10}N_7O_4S_2Cl$: C, 32.71; H, 2.47; N, 24.28; S, 15.86. Found: C, 32.50; H, 2.25; N, 24.10; S, 15.50%.

1,3-*Bis*-(indol-3-yl-methylideneamino)guanidine hydrochloride 11c

Crystallized from MeOH; yield 91%; m.p. 280ºC; IR (KBr): 3447 (-NH), 1658 (C=N), 1523 and 1437 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 7.18-7.21 (t, 2H, Ar), 7.23-7.26 (t, 2H, Ar), 7.47-7.49 (d, 2H, Ar), 7.89 (bs, 2H, 2 × – NH exch), 7.96-7.98 (t, 2H, Ar), 8.36-8.38 (d, 2H, Ar), 8.57 (s, 2H, 2 × =CH-), 11.61 (bs, 2H, 2 × –NH, exch), 11.83 (bs, 2H, NH.HCl, exch); GC-MS: No M^+ ion peak observed but other peaks obtained i.e. *m/z* 184 ($C_{10}H_8N_4$, 7.08%), 159 ($C_9H_9N_3$, 1.48%), 143 ($C_9H_7N_2$, 15.74%), 142 ($C_9H_6N_2$, 100%), 116 (C_8H_6N, 10.65%), 115 (C_8H_5N, 50.22%); Anal. Calcd. for $C_{19}H_{18}N_7Cl$: C, 60.07; H, 4.74; N, 25.82. Found: C, 59.95; H, 4.70; N, 25.61%.

1,3-*Bis*-(butan-2-ylideneamino)guanidine hydrochloride 11d

Crystallized from MeOH; yield 94%; m.p. 100ºC; IR (KBr): 3472 & 3372 (-NH), 1685 (C=N), 1515 and 1449 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 1.06-1.10 (m, 6H, 2 × $–CH_3$),1.97 (s, 6H, 2 × $–CH_3$), 2.30-2.51 (m, 4H, 2 × $–CH_2$-), 8.08 (bs, 2H, 2 × –NH, exch), 10.99 (bs, 2H, NH.HCl, exch); GC-MS *m/z* 198 (MH^+, 6.22%), 197($M^{+\cdot}$, 10.08%); Anal. Calcd. for $C_9H_{20}N_5Cl$: C, 46.25; H, 8.56; N, 29.97. Found: C, 46.01; H, 8.40; N, 29.59%.

1,3-*Bis*-(phenylethylideneamino)guanidine hydrochloride 11e

Crystallized from MeOH; yield 61%; m.p. 250ºC; IR (KBr): 3420 (-NH), 1670 (C=N), 1496 and 1444 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ: 2.47 (s, 6H, 2 × $–CH_3$), 7.44 -7.47 (m, 6H, Ar), 8.05-8.06 (m, 4H, Ar), 8.70 (bs, 2H, 2 × –NH, exch), 11.35 (bs, 2H, NH.HCl, exch); GC-MS: *m/z* 294 (MH^+, 2.59%), 293 ($M^{+\cdot}$, 13.78%), 292 ($M^{+\cdot}$- $H^{\cdot}$, 7.16 %); Anal. Calcd. for $C_{17}H_{20}N_5Cl$: C, 61.91; H, 6.06; N, 21.24. Found: C, 61.85; H, 6.00; N, 21.01%.

1,3-*Bis*-(*p*-chlorophenylethylideneamino)guanidine hydrochloride 11f

Crystallized from MeOH; yield 83%; m.p. >290ºC; IR (KBr): 3419 & 3235 (-NH), 1666 (C=N), 1490 and 1399 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.51 (s, 6H, 2 × $–CH_3$), 7.48-7.53 (d, 4H, Ar), 8.07-8.11 (d, 4H, Ar), 8.78 (bs, 2H, 2 × –NH, exch), 11.65 (bs, 2H, NH.HCl, exch); GC-MS : No M^+ ion peak observed but other peaks were obtained i.e. *m/z* 250 ($C_{11}H_{13}N_5Cl$, 6.05%), 209 ($C_9H_{10}N_4Cl$, 4.20%), 194 ($C_9H_9N_3Cl$,13.32%), 167 ($C_8H_8N_2Cl$, 24.81%), 152 (C_8H_7NCl, 100.00%), 137 (C_7H_4NCl , 27.29%), 111 (C_6H_4Cl, 85.82%); Anal. Calcd. for $C_{17}H_{18}N_5Cl_3$: C, 51.19; H, 4.51; N, 17.56. Found: C, 51.00; H, 4.25; N, 17.42%.

1,3-*Bis*-(*p*-cyanophenylethylideneamino)guanidine hydrochloride 11g

Crystallized from MeOH; yield 95%; m.p. 282ºC; IR (KBr): 3435 (-NH), 2223 (-C=N),1662 (C=N), 1491 and 1458 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.47 (s, 6H, 2 × $–CH_3$), 7.92-7.94 (d, 4H, Ar), 8.26-8.27 (d, 4H, Ar), 8.93 (bs, 2H, 2 × –NH, exch), 11.92 (bs, 2H, NH.HCl, exch); GC-MS: No M^+ ion peak observed but other peaks obtained i.e. *m/z* 143 ($C_9H_7N_2$, 6.74%), 142 ($C_9H_6N_2$, 100.00%); Anal. Calcd. for $C_{19}H_{18}N_7Cl$: C, 60.07; H, 4.74; N, 25.82. Found: C, 60.00; H, 4.50; N, 25.60%.

1,3-*Bis*-(*p*-methoxyphenylethylideneamino)guanidine hydrochloride 11h

Crystallized from MeOH; yield 65%; m.p. 180ºC; IR (KBr): 3430 and 3235 (-NH), 1635 (C=N), 1511

and 1416 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.39 (s, 6H, 2 × $–CH_3$), 3.81 (s, 6H, 2 × $–OCH_3$), 6.96-7.00 (t, 4H, Ar), 7.98-8.02 (t, 4H, Ar), 8.55 (bs, 2H, 2 × –NH, exch), 11.38 (bs, 2H, NH.HCl, exch). GC-MS : No M^+ ion peak observed but other peaks were obtained i.e. *m/z* 246 ($C_{12}H_{16}N_5O$, 14.54%), 205 ($C_{10}H_{13}N_4O$, 3.05%), 190 ($C_{10}H_{12}N_3O$, 8.66%), 163 ($C_9H_{11}N_2O$, 18.34%), 148 ($C_9H_{10}NO$, 100.00%), 133 (C_8H_7NO, 30.74%), 107 (C_7H_7O , 12.15%). Anal. Calcd. for $C_{19}H_{24}N_5O_2Cl$: C, 58.53; H, 6.16; N, 17.97. Found: C, 58.25; H, 6.01; N, 17.82%.

1,3-*Bis*-(3-pyridylethylideneamino)guanidine hydrochloride 11i

Crystallized from MeOH; yield 95%; m.p. 280ºC; IR (KBr): 3527 (NH), 1624 (C=N), 1475 and 1426 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.48 (s, 6H, 2 × -CH_3), 7.48-7.51 (q, 2H, Ar), 8.43-8.45 (d, 2H, Ar), 8.64-8.65 (q, 2H, Ar), 8.84 (bs, 2H, 2 × –NH exch), 9.261-9.264 (d, 2H, Ar), 11.90 (bs, 2H, NH.HCl, exch); GC-MS *m/z* 296 (MH^+, 0.33%), 295 ($M^{+\cdot}$, 4.68%); Anal. Calcd for $C_{15}H_{18}N_7Cl$: C, 54.29; H, 5.42; N, 29.56. Found: C, 53.90; H, 5.29; N, 29.30%.

1,3-*Bis*-(4-pyridylethylideneamino)guanidine hydrochloride 11j

Crystallized from MeOH; yield 96%; m.p. 275ºC; IR (KBr): 3468 (NH), 1624 (C=N), 1597, 1503 and 1412 (Ar) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.46 (s, 6H, 2 × -CH_3) , 8.03-8.05 (d, 4H, Ar), 8.68-8.69 (d, 4H, Ar), 8.90 (bs, 2H, 2 × –NH, exch), 12.07 (bs, 2H, NH.HCl, exch); GC-MS *m/z* 296 (MH^+, 1.08%), 295 ($M^{+\cdot}$, 6.44%); Anal. Calcd. for $C_{15}H_{18}N_7Cl$: C, 54.29; H, 5.42; N, 29.56. Found: C, 54.01; H, 5.39; N, 29.28%.

Anti-inflammatory activity

Paw oedema inhibition test was used on albino rats of Charles Foster strain by adopting the method of Winter[21]. Groups of five animals of both sexes (body weight 120-160 g), pregnant females excluded were given a dose of a test compound. Thirty minutes later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1-3 hr later. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not with test compounds) at the same time intervals and percent inhibition values were calculated by the formula given below.

$$\% \text{ Anti-inflammatory activity} = [1-D_t / D_c] \times 100.$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively.

Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis *et al*[22]. Groups of five mice (body weight 20-30 g) of both sexes, pregnant female excluded, were given a dose of a test compound. Thirty minutes later, the animals were injected intraperitoneally with 0.25 mL/ mouse of 0.5% acetic acid solution and writhes were counted during the following 60 min. The mean number of writhes for each experimental group and percent decrease compared with control group (five mice not treated with test compounds) were calculated.

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References

1 Gacche R N, Gond D S, Dhole N A & Dawane B S, *J Enzyme Inhib Med Chem*, 21, **2006**, 157.
2 Vazzanaa I, Terranova E, Mattioli F & Sparatorea F, *ARKIVOC*, (5), **2004,** 364.
3 Reedy E P & Reddy M V R, *PCT Int. Appl. WO 2003049698*, **2006**; *Chem Abstr*, **2006,** 369918.
4 Ranatunge R R, Garvey D S & Richardson S K, *U S Patent 2004006 133*, **2004,** *Chem Abstr* 140, **2004**, 77144.
5 Bramm E, Binderup L &Arrigoni-Martelli E, *Agents Actions* 11, **1981**, 402.
6 More P G, Bhalvankar R B & Pattar S C, *J Indian Chem Soc*, 78, **2001**, 474.
7 Li C, Lewis M.R, Gilbert A B, Noel M D, Scoville D H, Allmann G W & Savage PB, *Antimicrol Agents Chemother*, 43, **1999**, 1347.
8 Golebiewski W M & Cholewinska M, *Polish J Applied Chem*, 47, **2003** 137.
9 Jana G H, Jain S, Arora S K & Sinha N, *Bioorg Med Chem Lett*, 15, **2005**, 3592.
10 Desai S B, Desai P B & Desai K R, *Heterocycl Commun*, 7, **2001,** 83.

11 Brzozowski Z, Saczewski F & Slawinski J, *Eur J Med Chem*, 42, **2007**, 1218.
12 Krungkrai J, Scozzafava A, Reungprapavut S, Krungkrai S R, Rattanajak R, Kamchonwongpaisan S & Supuran C T, *Bioorg Med Chem,*13, **2005**, 483.
13 Calas M, Ouattara M, Piquet G, Ziora Z, Bordat Y, Ancelin M L, Escale R & Vial H, *J Med Chem,* 50, **2007**, 6307.
14 Aydogan F, Öcal, N. Turgut Z & Yolacan C, *Bull Korean Chem Soc,* 22, **2001**, 476.
15 Sondhi, S M, Singh N, Lahoti A M, Bajaj, K, Kumar A, Lozech O & Meijer L, *Bioorg Med Chem,* 13, **2005**, 4291.
16 Sondhi S M, Jain S, Dinodia M, Shukla, R & Raghubir R, *Bioorg Med Chem,* 15, **2007**, 3334.
17 Sondhi S M, Dinodia M, Singh J & Rani R, *Current Bioactive Compounds,* 3, **2007**, 91.
18 Kappe C O & Dallinger D, *Nat Rew Drug Discov,* 5, **2006**, 51.
19 Lidstrom P, Tierney J, Wathey B & Westman J, *Tetrahedron,* 57, **2001**, 9225
20 Liu J.-F, Ye P, Zhang B, Bi G, Sargent K, Yu L, Yohannes D & Baldino C M, *J Org Chem,* 16, **2005**, 6339.
21 Winter C A, Risley E A & Nuss G W, *Proc Soc Exp Bio Med,* 111, **1962**, 544
22 Davies J E, Kellett D N & Pennington J C, *Arch. Int Pharmacodyn Ther,* 221 **1976**, 274.