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, analgesic1,5, antimicrobial6,7, antifungal8,9, antitumor10,11 and antimalarial12,13 etc. Schiff bases are also employed as ligands for the complexation of metal ions34. Tempted by a variety of biological activities exhibited by Schiff bases, hydrazone and guanidine derivatives and in continuation of earlier efforts15-17 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 irradiation18-20 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 (1H-Indol-3-yl-methylene)-[3-(4-\{3-[(1H-indol-3-yl-methylene)-amino]-propyl]piperazin-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
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'-\left(1-(6-(1-(\text{phenylsulfonamidoimino)}\text{pyridine-2-yl)}\text{ethylidene) benzenesulfono-hydrazide} \ 8a \quad \text{(Scheme II)} \text{in 50% yield. Condensation of 2,6-diacetyl pyridine with 4-methyl benzene sulfonylhdyrazide and 4-methoxy benzenesulfonyl hydrazide gave products} \ 8b \text{ and } 8c \text{(Scheme II) respectively. Structures assigned to} \ 8a, 8b \text{ and } 8c \text{ are supported by spectral and analytical data reported in experimental section.}

Condensation of furfural $9a \text{(Scheme II)} \text{ with 1,3-diaminoguanidine monohydrochloride} \ 10a \text{(Scheme II) \text{ in 2:1 molar ratio was carried out by heating under reflux in methanol for five hr. Solvent was removed under reduced pressure to give crude product} \ 11a \text{ which was purified by crystallization from methanol to give pure product} \ 11a, \ i.e. \ 1,3-\text{bis-(furan-2-yl-}}$
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'-chloroacetophenone 9f, 4-acetyl benzonitrile 9g, 4-methoxyacetophenone 9h, 3-acetylpyridine 9i, and 4-acetylpyridine 9j with diaminoguanidine hydrochloride 10 gave condensation products 11a-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 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
and 63% anti-inflammatory activity respectively, whereas phenylbutazone showed 17 and 63% anti-inflammatory activity at 25 mg/ kg p.o. and 100 mg/ kg p.o. respectively. Compounds 3b and 11e exhibited anti-inflammatory activity comparable to phenylbutazone.

Analgesic activity 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.

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

<table>
<thead>
<tr>
<th>Compd tested</th>
<th>Dose mg/kg p.o.</th>
<th>Anti-inflammatory activity (%)</th>
<th>Analgesic activity (%)</th>
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<tr>
<td>3a</td>
<td>50</td>
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<tr>
<td>3b</td>
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<td>62</td>
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<td>3c</td>
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<td>8b</td>
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<td>8c</td>
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<td>11j</td>
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<td>Phenyl butazone</td>
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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 stereochimically.

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. 1H NMR were recorded on a Bruker WH-300/Bruker av-500 spectrometer in D5-15% (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. 75°C. FT-IR spectrum of 3a show absorption band at 1648 cm$^{-1}$ (due to C=O). While interpreting $^1$H NMR of starting material with the help of $^1$H NMR of starting material, the peak positions were assigned with the help of $^1$H NMR of starting material and the assigned peak positions were interpreted $^1$H NMR of starting material. Similarly compounds 3c-d were synthesized.

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

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]undecane 3,9-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. 185°C. IR (KBr): 1633 (C=N) and 1575 (Ar) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 1.60-1.80 (m, 8H, 4 × -CH$_2$-, C$_4$, C$_{18}$, C$_5$, C$_{17}$), 2.21 (s, 6H, 2 × -CH$_3$), 3.46-3.52 (m, 4H, 2 × -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), 8.51-8.65 (d, 2H, Ar); FAB-MS m/z 481 (MH$^+$, 100%); Anal. Calcd. for C$_{27}$H$_{36}$N$_4$O$_4$: C, 67.00; H, 7.50; N, 11.51%.

(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 3d

Crystallized from MeOH; yield 57%; m.p. 110°C; IR (KBr): 3409 (-NH-) cm$^{-1}$, 1637 (C=N), and 1530 (Ar), 1132 (SO$_2$) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$ + CDCl$_3$): $\delta$ 1.73-1.89 (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$_{16b}$), 7.49-7.496 (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$_4$O$_4$: C, 67.00; H, 7.50; N, 11.51%.

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

**Synthesis of (1H-indol-3-ylmethylene)-[3-4-[3-(1H-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. 85°C. FT IR of 5a show absorption bands at 3412 (=-NH-) cm$^{-1}$, 1637 (C=N), and 1530 (Ar), 1132 (SO$_2$) cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$ + CDCl$_3$): $\delta$ 1.86-1.95
(m, 4H, 2 × -CH= , C4, C13), 2.47-2.52 (m, 12H, 6 × -CH2-, C5, C7, C11, C8, C10, C12), 3.59-3.63 (t, 4H, 2 × -CH2-, C3, C14), 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 C28H34N6: 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]piperazin-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-d6 + CDCl3): δ 1.92-2.01 (m, 4H, 2 × -CH2-, C4, C13), 2.36 (s, 6H, 2 × -CH3), 2.49-2.73 (m, 12H, 6 × -CH2-, C5, C7, C11, C8, C10, C12), 3.54-3.58 (t, 4H, 2 × -CH2-, C3, C14), 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 C24H34N6: C, 70.93; H, 8.37; N, 20.68. Found: C, 71.09; 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-d6): δ 1.93-2.00 (q, 4H, 2 × -CH2-, C4, C13), 2.23 (s, 6H, 2 × -CH3), 2.36-2.52 (m, 12H, 6 × -CH2-, C5, C7, C11, C8, C10, C12), 3.51-3.56 (t, 4H, 2 × -CH2-, C3, C14), 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 C23H34N6: 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-(phenylsulfonylimino)-ethyl)pyridine-2-yl)methylene)benzenesulfonylamide 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-d6 + D2O): δ 2.20 (s, 6H, 2 × –CH3), 7.55 -7.62 (m, 6H, Ar), 7.70-7.80 (m, 3H, Ar), 7.90-8.00 (dd, 4H, Ar), 8.45; 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)methylene)benzenesulfonylamide 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-d6 + D2O): δ 2.23 (s, 6H, 2 × -CH3), 2.35 (s, 6H, 2 × -CH3), 7.35-7.45 (d, 4H, Ar), 7.75-7.79 (m, 7H, Ar); GC-MS m/z 499 (M+, 30%). Anal. Calcd for C23H25N5S2O4: 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-((4-methoxyphenylsulfonyl)amino)ethyl)pyridine-2-yl)methylene)benzenesulfonylamide 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-d6): δ 2.32 (s, 6H, 2 × -CH3), 3.88 (s, 6H, 2 × -OCH3), 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, exh, 2 × -NH); GC-MS m/z 531(M+, 13%); Anal. Calcd for C23H25N5S2O6: 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-methylene)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. 80°C; 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-d₆); 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⁺, 1.28%), 246 (MH⁺, 12.42%), 245 (M⁻, 100.00%); Anal. Calcd. for C₁₁H₁₂N₂O₂Cl: 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. 170°C; IR (KBr): 3434 (-NH), 1623 (C=N), 1589, 1531 and 1499 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); 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 (C₇H₇N₂O₂S, 0.92%); 128 (C₆H₅NO₂S, 0.91%). Anal. Calcd. for C₁₁H₁₂N₂O₂S: 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. 280°C; IR (KBr): 3447 (-NH), 1658 (C=N), 1523 and 1437 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); 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 (C₁₀H₁₀N₄, 7.08%), 159 (C₉H₇N₃, 4.85%), 143 (C₈H₆N₂, 1.48%), 142 (C₈H₅N₂ , 100.00%), 116 (C₈H₅N, 10.65%), 115 (C₈H₅N, 50.22%); Anal. Calcd. for C₁₀H₁₈N₇Cl: 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. 100°C; IR (KBr): 3472 & 3372 (-NH), 1685 (C=N), 1515 and 1449 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); δ: 1.06-1.10 (m, 6H, 2 × −CH₃),1.97 (s, 6H, 2 × −CH₃), 2.30-2.51 (m, 4H, 2 × −CH₂-), 8.08 (bs, 2H, 2 × −NH, exch), 10.99 (bs, 2H, NH.HCl, exch); GC-MS m/z 198 (MH⁺, 6.22%), 197 (M⁻, 10.08%); Anal. Calcd. for C₉H₂₀N₅Cl: 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. 250°C; IR (KBr): 3420 (-NH), 1670 (C=N), 1496 and 1444 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); δ: 2.47 (s, 6H, 2 × −CH₃), 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⁻, 13.78%), 292 (M⁻ - H, 7.16%); Anal. Calcd. for C₁₁H₁₂N₂Cl: 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. >290°C; IR (KBr): 3419 & 3235 (-NH), 1666 (C=N), 1490 and 1399 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); δ: 2.51 (s, 6H, 2 × −CH₃), 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 (C₁₁H₁₃N₂Cl, 6.05%), 209 (C₁₀H₁₀N₂Cl, 4.20%), 194 (C₉H₇N₂Cl ,13.32%), 167 (C₈H₅N₂Cl, 24.81%), 152 (C₈H₅NCl, 100.00%), 137 (C₇H₆NCl , 27.29%), 111 (C₈H₇Cl, 85.82%); Anal. Calcd. for C₁₁H₁₃N₂Cl: 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. 282°C; IR (KBr): 3435 (-NH), 2223 (-C=N),1662 (C=N), 1491 and 1458 (Ar) cm⁻¹; 1H NMR (500 MHz, DMSO-d₆); δ: 2.47 (s, 6H, 2 × −CH₃), 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 (C₈H₈N₂, 6.74%), 142 (C₈H₇N₂, 100.00%); Anal. Calcd. for C₁₁H₁₃N₂Cl: 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. 180°C; IR (KBr): 3430 and 3235 (-NH), 1635 (C=N), 1511
and 1416 (Ar) cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\): 2.39 (s, 6H, \(2 \times -\text{CH}_3\)), 3.81 (s, 6H, \(2 \times -\text{OCH}_3\)), 6.96-7.00 (t, 4H, Ar), 7.98-8.02 (t, 4H, Ar). 8.55 (bs, 2H, \(2 \times -\text{NH}, \text{exch}\)), 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\(_5\)O, 14.54%), 205 (C\(_{10}\)H\(_{13}\)N\(_4\)O, 8.66%), 163 (C\(_{8}\)H\(_{10}\)NO, 34.54%), 148 (C\(_{9}\)H\(_{10}\)NO, 100.00%), 133 (C\(_{8}\)H\(_{7}\)NO, 30.74%), 107 (C\(_{7}\)H\(_{7}\)O, 12.15%). Anal. Calcd. for C\(_{19}\)H\(_{24}\)N\(_5\)O\(_2\)Cl: 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\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\): 2.48 (s, 6H, \(2 \times -\text{CH}_3\)), 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, \(2 \times -\text{NH}, \text{exch}\)), 9.261-9.264 (d, 2H, Ar), 11.90 (bs, 2H, NH.HCl, exch); GC-MS m/z 296 (MH\(^+\), 0.33%), 295 (M\(^+\), 6.44%); Anal. Calcd. for C\(_{15}\)H\(_{18}\)N\(_7\)Cl: 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\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\): 2.46 (s, 6H, \(2 \times -\text{CH}_3\)), 8.03-8.05 (d, 4H, Ar), 8.68-8.69 (d, 4H, Ar), 8.90 (bs, 2H, \(2 \times -\text{NH}, \text{exch}\)), 12.07 (bs, 2H, NH.HCl, exch); GC-MS m/z 296 (MH\(^+\), 1.08%), 295 (M\(^+\), 6.44%); Anal. Calcd. for C\(_{15}\)H\(_{18}\)N\(_7\)Cl: 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\(^2\). 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.

\[
\text{% Anti-inflammatory activity} = \frac{|D_t - D_c|}{D_c} \times 100.
\]

\(D_t\) 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 \(^et\ al\)\(^2\). 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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