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Original article

Synthesis of 6- and 9-alkylaminomethyl furoflavones as gastroprotective agents

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Abstract

The synthesis of 9- and 6-alkylaminomethyl furoflavones **5a**, **b**, **9a–c**, **13a**, **b**, **15a–g** and **18** from the naturally occurring chromones visnagin and khellin. Gastroprotective potency of these compounds in the ethanol damage model was determined. The results indicate that, through appropriate substitution, furoflavones can be obtained that are gastroprotective.

Keywords: Mannich bases; Furoflavones; Furobenzopyran-5-ones; Gastroprotective potency; Claisen reaction

1. Introduction

The development of safe and effective drug, capable of preventing stomach damage induced by NSAIDs or other gastric-damaging substances [1–3], represents an important goal of medicinal research [4–6]. Flavonic compounds (2-phenyl-4*H*-benzopyran-4-one derivatives) either natural or synthetic exhibit various biological activities, for example gastroprotective, antioxidant, anti-inflammatory and antitumor activities [7–13]. The simple unsubstituted flavone was found to be potent gastroprotective agent in an ethanol-induced gastric damage model in rats [14]. It is found that in the 4-benzopyrone moiety, substitution in the 5-position with a methoxy group provided a high level of gastroprotection that was comparable to that of unsubstituted flavone. Additionally a number of substituted 5-methoxy flavones have been prepared and retained the gastroprotective properties [9]. On the other hand, furoflavones are not tested for the gastroprotective activity. Thus in the present study two series of alkoxylated (4-methoxy) and one series of hydroxylated (4-hydroxy) furoflavones, substituted at different positions (6 and 9) with alkylaminomethyl groups were synthesized and evaluated for their gastroprotective activity in order to expand structure–activity relationship and study the effect of structural modulation around the flavone nucleus on its gastroprotective properties.

2. Chemistry

Conversion of the natural furochromone **1a** (visnagin) to the required 9-alkylaminomethyl furoflavones **5a**, **b**, **9a–c**, **11d–e** and **13a**, **b** was accomplished as depicted in Schemes 1 and 2. Visnagin **1a** and Khellin **1b** undergo typical β-diketone cleavage by alkali to afford the benzofuran derivatives **2a** and **2b** [15]. On subjecting **2a** to Mannich reaction using secondary amines and paraformaldehyde, the 7-alkylaminomethyl benzofuran derivatives **3a–b** were formed and substitution was previously proved to be in the benzenoid ring and not at the acetyl group [16]. The β-diketones **4a**, **b** have been synthesized through Claisen condensation of **3a**, **b** with ethyl nicotinate. Compounds **4a**, **b** were converted to the corresponding furoflavones **5a**, **b** by acid catalyzed cyclodehydration with sulphuric acid, Scheme 1. On the other hand the furoflavones **11a–e** in which the aromatic residue is phenyl or substituted phenyl have been synthesized through

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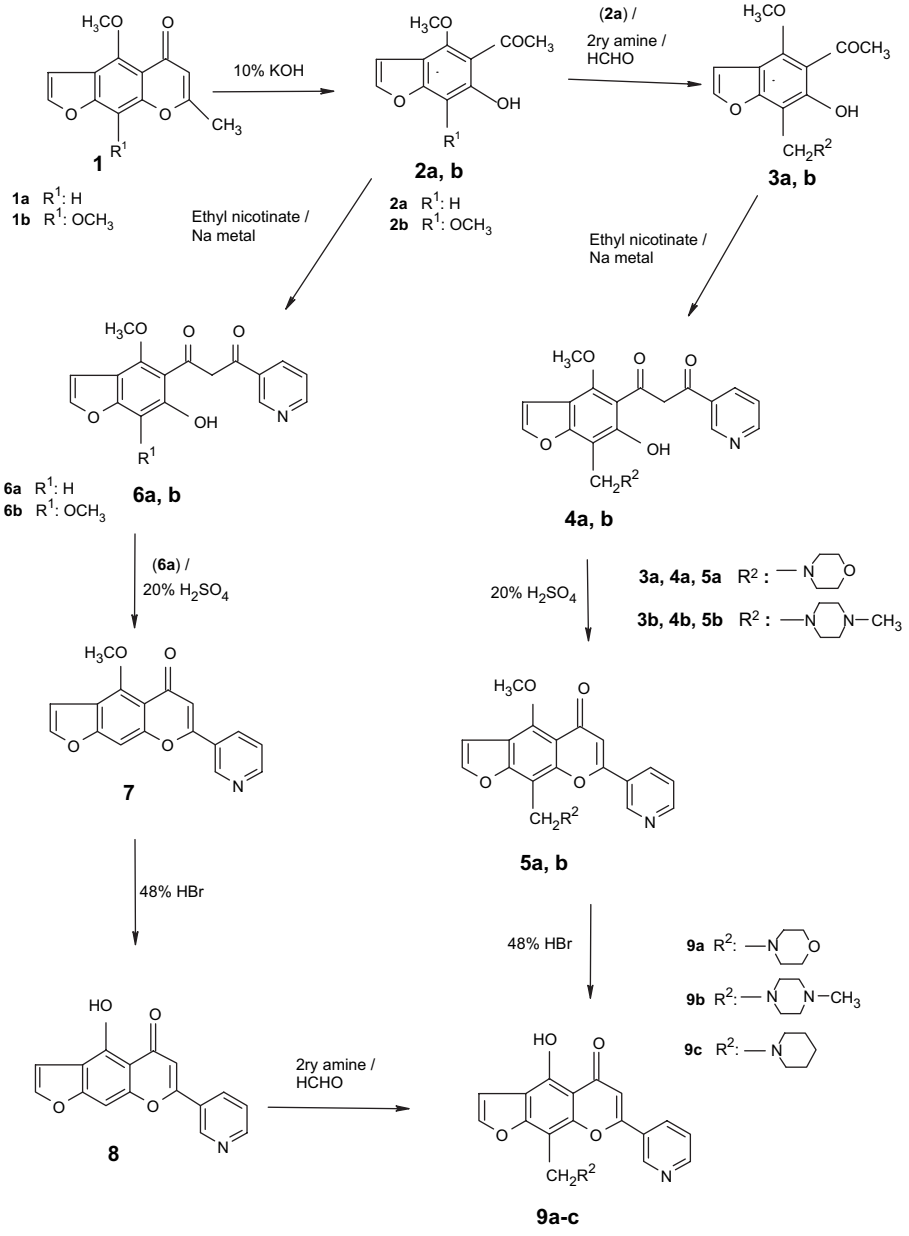
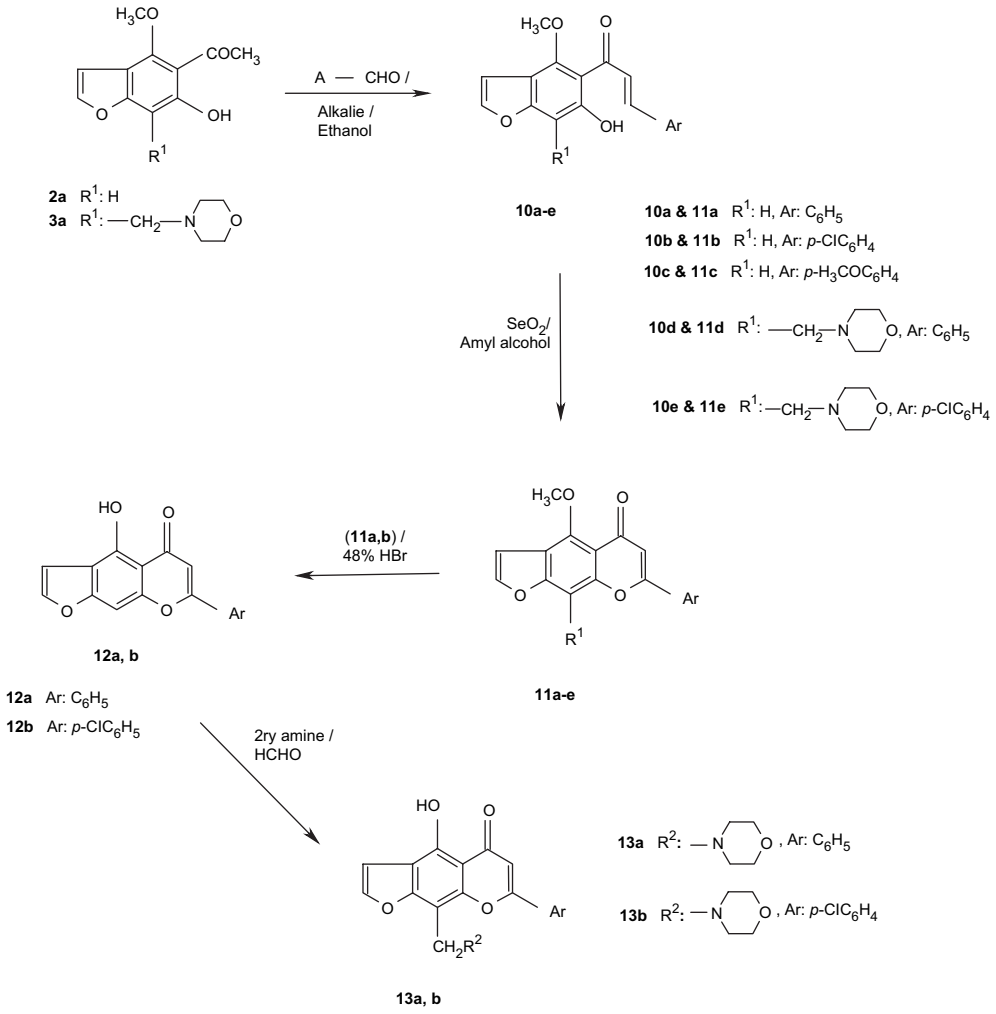


Scheme 1.

condensation of **2a** or **3a** with the corresponding aromatic aldehydes to afford the α,β-unsaturated ketone derivatives **10a–e** followed by oxidative cyclization with SeO_2, Scheme 2. The 4-hydroxylated furoflavones **9a–c** and **13a**, **b** were obtained through demethylation of the 4-methoxy furoflavones **5a**, **b**, **7** and **11a–c**, respectively, with 48% HBr followed by application of Mannich reaction, Schemes 1 and 2. Compounds **13a**, **b** were obtained from **11a**, **b**, respectively. Similar methodology from **2a** to afford compound **8**. The furoflavone **8** was converted to **9a–c** by Mannich reaction. Attempts to introduce the alkylaminomethyl group directly into the 6-position of the furoflavones **7** and **11a–c** failed, consequently the 6-alkylaminomethyl derivatives **15a–g** have been obtained by applying Mannich reaction to the acylbenzofuran **6a** and **6b** followed by cyclization to the corresponding furoflavones **15a–g** with sulphuric acid, Scheme 3. On the other hand, the 6-alkylaminomethyl furoflavone **18** where the aromatic residue is phenyl was obtained by controlled alkaline hydrolysis of **11a** to give the β-diketone **16** [17] which was subjected to Mannich reaction to give **17** followed by cyclization with sulphuric acid, Scheme 4.

3. Pharmacology, results, discussion and conclusion

Fifteen representative examples of the synthesized compounds are initially screened in the rat ethanol-induced damage model, a well-established and convenient model for the evaluation of gastric protection [18,19]. Gastroprotection data are listed in Tables 1–4.



Scheme 2.

3.1. Statistics

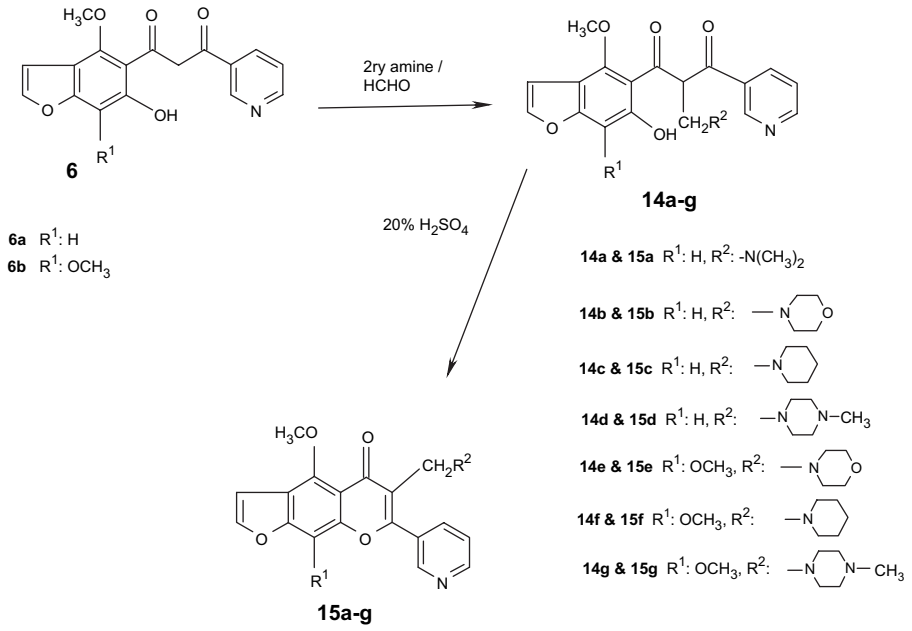
Data were summarized as mean, standard deviation (SD) and standard error (SE) and were compared using one-way analysis of variance (ANOVA). Significant ANOVA was followed by least significant difference (LSD) per-wise comparison test. P value <0.05 was considered statistically significant. All calculations were made on SPSS statistical software, Tables 1–4.

3.2. Results

All the tested compounds exhibited gastroprotective activity. As regards the ulcer number, compounds **15g** and **11c** showed the least number of ulcer number (18.8, 19.7, respectively) and control (33.0). However, there is no statistically significant difference in the ulcer number among all the studied compounds including the control ($P = 0.114$), Table 1. On the other hand, the mean ulcer index was highly significantly different from the control group ($P = 0.045$) in the case of compounds **11c**, **15g**, **18**, **5b** and **15a** (24.0, 28.2, 29.6, 29.7 and 31.0, respectively). While **11b**, **12b**, **11a** and **15e** showed less statistically significant difference compared to the control group (33.2, 33.5, 34.8 and 36.0, respectively), Table 2. Comparison of each tested compound with the control and all other compounds showed that there was highly significant difference between **11c** with **13b**, **5a**, **11d**, **12a** or **13a** while there was less statistical difference between **15g** with **13b**, Table 3. Regarding the preventive index (PI) of the tested compounds, it ranged from 16 (**13b**) to 53% (**11c**) but it did not attain statistical significance, Table 4.

3.3. Discussion

In the benzopyrone portion of the furoflavone system, the type of aromatic substitution at 7-position affected the gastroprotective effect as shown in Tables 1–4. The *p*-methoxyphenyl derivative **11c** was more active than the *p*-chlorophenyl **11b** which was more active than the phenyl derivative **11a**. The presence of 9-alkylaminomethyl substituent in these compounds decreased the activity of **11d**, **e**, while the presence of 6-alkylaminomethyl substituent increased the activity (compound **18** showed more activity than **11a**). When the aromatic group in position 7 was pyridinyl, the activity was slightly

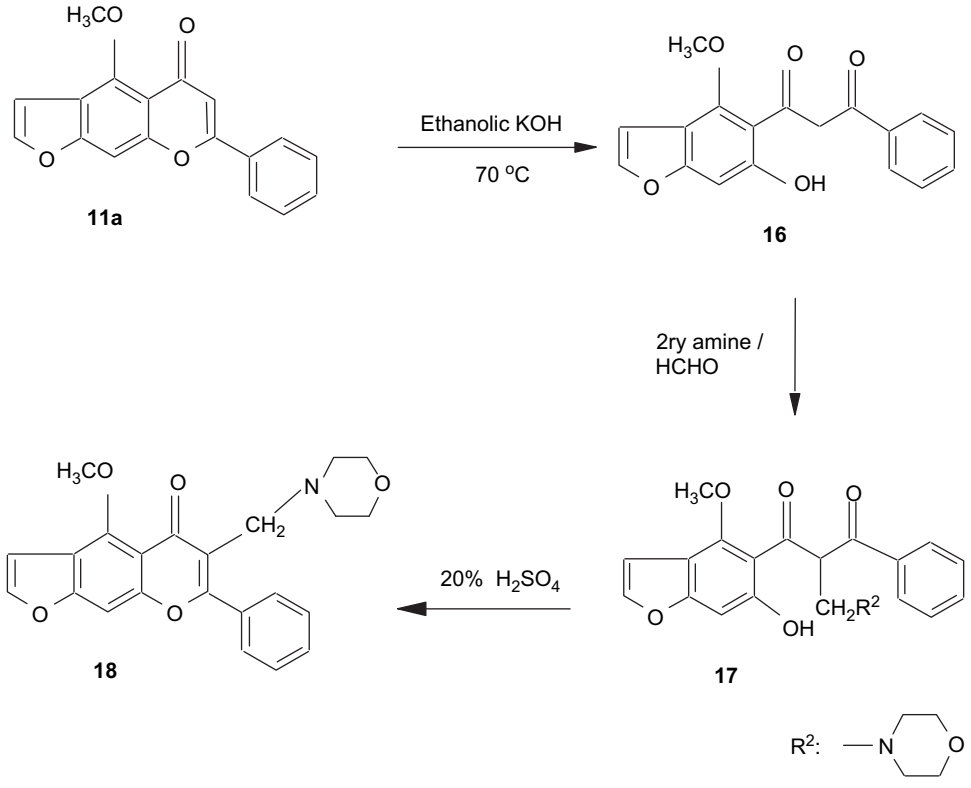


Scheme 3.

decreased (compounds **5a**, **15a**) except in the case of 9-*N*-methylpiperazinomethyl derivative **5b** which showed promising gastroprotective activity. It was found that the presence of methoxy group showed great effect on the activity. Substitution at 4-position with methoxy group (compounds **11a–e**) enhanced the gastroprotective activity, in contrast to 4-hydroxy derivatives **12a**, **b**, **13a**, **b** which showed markedly decrease in activity. Substitution with another methoxy group **15g** produced a potent level of gastroprotection.

3.4. Conclusion

In summary, we found that the presence of methoxy group (either in 4, 9 or 7-position as methoxyphenyl) and through the



Scheme 4.

Table 1
Effect of the studied compounds on ulcer number values ($P = 0.114$)

Compound	Number	Mean	SD	SE	Minimum	Maximum
Control	6	33.0	6.7	2.7	25	41
5a	5	25.0	4.2	1.9	19	30
5b	6	23.7	6.1	2.5	17	34
11a	6	23.7	8.0	3.3	10	33
11b	6	25.5	5.7	2.3	19	33
11c	6	19.7	4.2	1.7	14	27
11d	6	27.8	8.7	3.6	18	41
11e	5	26.0	4.6	2.1	20	32
12a	6	25.5	10.9	4.5	13	43
12b	6	22.2	4.7	1.9	17	30
13a	6	26.5	10.0	4.1	19	43
13b	6	28.5	7.3	3.0	21	39
15a	6	21.2	8.0	3.3	13	34
15e	6	24.0	3.5	1.4	19	28
15g	6	18.8	7.8	3.2	8	27
18	5	21.8	4.4	2.0	18	29

appropriate substitution in 6-position with alkylaminomethyl group, furoflavones exhibited good gastroprotective activity in the ethanol damage model.

4. Experimental protocols

4.1. Chemistry

Melting points are uncorrected and determined in one end open capillary tubes using Gallen Kamp melting point apparatus (MFB-595-010M). Microanalysis was carried out at the microanalytical unit, Faculty of Science, Cairo University. IR spectra were determined using potassium bromide discs on Shimadzu Infrared Spectrometer (IR-435-Kyoto, Japan), FTIR 1650 (Perkin Elmer) and Genesis II FTIR™ Spectrometer (Mottson, Madison, USA). ^{1}H NMR spectra were determined using Joel NMR Varian Gemini 200 MHz Spectrometer (Jeol, Tokyo, Japan) and Varian Mercury VX-300 MHz NMR Spectrometer (Oxford, England). Chemical shifts (δ) are given in parts per million (ppm) downfield from TMS as the internal

Table 2
Effect of the studied compounds on ulcer index values ($P = 0.045$)

Compound	Number	Mean (mm)	SD (mm)	SE (mm)	Min (mm)	Max (mm)
Control	6	50.7	8.8	3.6	39	62
5a	5	40.8	12.6	5.7	29	62
5b	6	29.7	7.6	3.1	21	41
11a	6	34.8	11.4	4.6	15	49
11b	6	33.2	11.7	4.8	18	50
11c	6	24.0	6.4	2.6	17	31
11d	6	39.8	16.0	6.5	18	62
11e	5	37.2	10.7	4.8	20	48
12a	6	38.3	16.5	6.8	19	65
12b	6	33.5	6.9	2.8	26	45
13a	6	37.5	17.2	7.0	17	64
13b	6	42.5	10.9	4.5	31	58
15a	6	31.0	12.9	5.3	18	51
15e	6	36.0	4.9	2.0	29	42
15g	6	28.2	11.7	4.8	12	40
18	5	29.6	10.7	4.8	14	43

Table 3
Comparison between ulcer index values of various compounds

	5a	**5b**	**11a**	**11b**	**11c**	11d	**11e**	**12a**	**12b**	**13a**	**13b**	**15a**	**15e**	**15g**	**18**
Control	0.164	0.002**	0.021*	0.011*	0.000**	0.110	0.059	0.069	0.012*	0.053	0.226	0.004**	0.031*	0.001**	0.004**
5a		0.117	0.398	0.280	0.019*	0.891	0.625	0.726	0.302	0.640	0.809	0.167	0.496	0.076	0.131
5b			0.443	0.603	0.400	0.133	0.287	0.199	0.569	0.246	0.059	0.843	0.347	0.823	0.992
11a				0.804	0.110	0.457	0.737	0.603	0.843	0.691	0.256	0.569	0.862	0.322	0.458
11b					0.175	0.322	0.567	0.443	0.960	0.519	0.167	0.747	0.673	0.457	0.613
11c						0.021*	0.064	0.035*	0.160	0.047*	0.007**	0.299	0.077	0.535	0.428
11d							0.709	0.823	0.347	0.728	0.691	0.191	0.569	0.085	0.149
11e								0.872	0.600	0.966	0.453	0.380	0.865	0.202	0.303
12a									0.472	0.901	0.535	0.277	0.728	0.133	0.217
12b										0.552	0.183	0.710	0.710	0.428	0.580
13a											0.457	0.335	0.823	0.167	0.264
13b												0.090	0.335	0.035*	0.070
15a													0.457	0.673	0.842
15e														0.246	0.365
15g															0.839

*Statistically highly significant, P value <0.05.
**Statistically highly significant, P value <0.01.

Table 4
Effect of the studied compounds on preventive index values ($P = 0.345$)

Compound	Number	Mean	SD	SE	Minimum	Maximum
5a	5	19.5	24.9	11.2	−22.4	42.8
5b	6	41.5	15.0	6.1	19.1	58.6
11a	6	31.3	22.4	9.1	3.3	70.4
11b	6	34.5	23.0	9.4	1.3	64.5
11c	6	52.6	12.5	5.1	38.8	66.4
11d	6	21.4	31.6	12.9	−22.4	64.5
11e	5	26.6	21.0	9.4	5.3	60.5
12a	6	24.3	32.6	13.3	−28.3	62.5
12b	6	33.9	13.6	5.6	11.2	48.7
13a	6	26.0	33.9	13.9	−26.3	66.4
13b	6	16.1	21.6	8.8	−14.5	38.8
15a	6	38.8	25.5	10.4	−0.7	64.5
15e	6	29.0	9.6	3.9	17.1	42.8
15g	6	44.4	23.0	9.4	21.1	76.3
18	5	41.6	21.1	9.5	15.1	72.4

standard. Mass spectra were recorded using Hewlett Packard Varian (Polo, USA) and Shimadzu Gas Chromatograph Mass spectrometer-QP 1000 EX (Japan). TLC were carried out using Art.DC-Plastikfolien, Kieselgel 60 F254 sheets (Merck), the developing solvents were $CCl_4/CH_3COOC_2H_5$ (9:1) or (4:1) and the spots were visualized by UV 366, 254 nm.

*4.1.1. 7-Alkylaminomethyl-6-hydroxy-4-methoxy-5-(3-pyridinylacetocarboxy) benzofuran **4a** and **4b** (Scheme 1, Tables 5–7)*

A solution of **3a** or **3b** (0.01 mol) in ethyl nicotinate (0.05 mol, 7.55 g) was treated with (0.025 mol, 0.57 g) powdered sodium (prepared under toluene). After the initial reaction subsided, the mixture was refluxed for 2 h. It was then left to stand overnight, treated with ice-water and extracted with ether. The aqueous solution, after being freed from ether by a stream of air was neutralized with dil. NH_4OH and extracted with $CHCl_3$. The chloroformic extract was filtered through dry Na_2SO_4 and the filtrate was concentrated under reduced pressure. The residue was crystallized from $CHCl_3$/ether to give **4a**, **b**. MS for **4b** *m/z* 423.0 (M^+).

*4.1.2. 9-Alkylaminomethyl-4-methoxy-7-(3-pyridinyl)-5H-furo-[3,2-g][1]benzopyran-5-ones **5a** and **5b** (Scheme 1, Tables 5–7)*

A solution of **4a** or **4b** (0.03 mol) in 20% H_2SO_4 (30 ml) was refluxed for 1 h. The reaction mixture was left to cool and neutralized with 5% $NaHCO_3$. The separated solid was filtered, washed with water, dried and crystallized from ethanol. MS for **5a** *m/z* 392.2 (M^+).

*4.1.3. 7-Aryl and 9-alkylaminomethyl-7-aryl-4-methoxy-5H-furo[3,2-g][1]benzopyran-5-ones **11a–e** (Scheme 2, Tables 5–7)*

A mixture of the propenone **10a–e** (0.01 mol) and selenium dioxide (0.03 mol, 3.3 g) in amyl alcohol (50 ml) was refluxed for 48 h. The solution was filtered to remove the precipitated selenium metal and the filtrate was concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and washed with water. The chloroformic extract was filtered through dry Na_2SO_4 and the filtrate was concentrated under reduced pressure. The product was crystallized from ethanol. MS for **11a** *m/z* 292.1 (M^+), **11e** *m/z* 425 (M^+).

*4.1.4. 7-Aryl-4-hydroxy-5H-furo[3,2-g][1]benzopyran-5-one-**8** and **12a–b** (Schemes 1 and 2, Tables 5–7)*

A mixture of **7**, **11a** or **11b** (0.01 mol) and 48% HBr (0.01 mol, 1.7 ml) in glacial acetic acid (10 ml) was refluxed for 1 h, cooled and left in a refrigerator for 48 h. The separated solid was filtered, dried and crystallized from ethanol (compound **8**) or acetic acid/water (compounds **12a**, **b**). MS for **8** *m/z* 279 (M^+), **12a** *m/z* 278 (M^+).

*4.1.5. 9-Alkylaminomethyl-7-aryl-4-hydroxy-5H-furo[3,2-g][1]-benzopyran-5-ones **9a–c** and **13a–b** (Schemes 1 and 2, Tables 5–7)*

To a solution of **8**, **12a** or **12b** (0.01 mol) in glacial acetic acid (10 ml), the amine hydrochloride (0.011 mol) and paraformaldehyde (0.02 mol, 0.6 g) were added and refluxed for 8 h, cooled and ice-water was added. The mixture was neutralized with dil. NH_4OH and the separated solid was filtered, dried and crystallized from acetic acid/water. MS for **9c** *m/z* 376 (M^+), **13b** *m/z* 411 (M^+).

*4.1.6. 6-Hydroxy-4-methoxy (or 4,7-dimethoxy)-5-(3-pyridinyl-2-alkylaminomethyl acetocarboxy) benzofuran **14a–g** (Scheme 3, Tables 5–7)*

To a solution of **6a** ($R^1 = H$) or **6b** ($R^1 = OCH_3$) (0.01 mol) in absolute ethanol (50 ml), the amine hydrochloride (0.011 mol) and paraformaldehyde (0.02 mol, 0.6 g) were added and refluxed for 24 h. Excess solvent was evaporated under reduced pressure, cooled and water was added. The mixture was neutralized with dil. NH_4OH and extracted with $CHCl_3$. The chloroformic extract was filtered through dry Na_2SO_4 and the filtrate was concentrated under reduced pressure. The residue was crystallized from $CHCl_3$/ether to give **14a–g**. MS of **14a** *m/z* 369 ($M^+ + 1$).

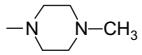
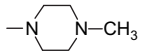
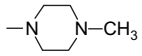
*4.1.7. 6-Alkylaminomethyl-7-aryl-4-methoxy (or 4,9-dimethoxy)-5H-furo[3,2-g][1]benzopyran-5-ones **15a–g** (Scheme 4, Tables 5–7)*

Use **14a–g** and proceed exactly as above to prepare compounds **5a**, **b**. The separated solid was crystallized using $CHCl_3$/ether. MS for **15a** *m/z* 349 ($M^+ - 1$), **15d** *m/z* 405.2 (M^+).

*4.1.8. 6-Hydroxy-4-methoxy-5-(3-phenyl-2-morpholinomethyl acetocarboxy) benzofuran **17** (Scheme 4, Tables 5–7)*

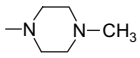
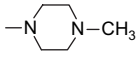
To a solution of **16** (0.01 mol, 3.1 g) in absolute ethanol (50 ml), morpholine hydrochloride (0.011 mol, 1.36 g) and paraformaldehyde (0.02 mol, 0.6 g) were added and applied the above procedure to prepare compounds **14a–g**. The residue was crystallized from $CHCl_3$/ether.

Table 5
Physical properties and microanalysis data of the new synthesized compounds

No.	R^1	R^2	Ar	Molecular formula (mol. wt.)	Melting point (°C)	Yield (%)	Microanalysis		
							Calculated (%)		Found (%)
4a	–		–	$C_{22}H_{22}N_2O_6$ (410)	147	65	C	64.39	64.40
							H	5.37	5.24
							N	6.83	7.00
4b	–		–	$C_{23}H_{25}N_3O_5$ (423)	138	75	C	65.25	65.75
							H	5.91	5.56
							N	9.93	9.60
5a	–		–	$C_{22}H_{20}N_2O_5$ (392)	300	55	C	67.35	67.70
							H	5.10	5.20
							N	7.14	6.60
5b	–		–	$C_{23}H_{23}N_3O_4$ (405)	300	60	C	68.15	68.50
							H	5.68	5.60
							N	10.37	10.30
8	–	–	–	$C_{16}H_9NO_4$ (279)	252	85	C	68.81	68.78
							H	3.22	3.36
							N	5.02	5.20
9a	–		–	$C_{21}H_{18}N_2O_5$ (378)	210	75	C	66.67	66.56
							H	4.76	4.40
							N	7.41	7.80
9b	–		–	$C_{22}H_{21}N_3O_4$ (391)	224	75	C	67.52	66.80
							H	5.37	5.98
							N	10.74	10.73
9c	–		–	$C_{22}H_{20}N_2O_4$ (376)	300	65	C	70.21	70.20
							H	5.32	5.10
							N	7.45	7.33
11a	H	–	C_6H_5	$C_{18}H_{12}O_4$ (292)	195	90	C	73.97	73.90
							H	4.12	4.19
11b	H	–	*p*-Cl C_6H_4	$C_{18}H_{11}ClO_4$ (326.5)	190	85	C	66.17	66.15
							H	3.37	3.45
11c	H	–	*p*-OCH_3 C_6H_4	$C_{19}H_{14}O_5$ (322)	160	85	C	70.81	71.20
							H	4.35	4.24
11d		–	C_6H_5	$C_{23}H_{21}NO_5$ (391)	190	60	C	70.59	70.75
							H	5.37	4.88
							N	3.58	3.44
11e		–	*p*-Cl C_6H_4	$C_{23}H_{20}ClNO_5$ (425.5)	174	70	C	64.86	64.86
							H	4.70	4.47
							N	3.29	3.51
12a	–	–	C_6H_5	$C_{17}H_{10}O_4$ (278)	237	90	C	73.38	73.41
							H	3.59	4.04
12b	–	–	*p*-Cl C_6H_4	$C_{17}H_9ClO_4$ (312.5)	234	85	C	65.28	65.02
							H	2.88	3.01
13a	–		C_6H_5	$C_{22}H_{19}NO_5$ (377)	196	65	C	70.03	70.07
							H	5.04	5.03
							N	3.71	3.70
13b	–		*p*-Cl C_6H_4	$C_{22}H_{18}ClNO_5$ (411.5)	300	70	C	64.16	64.00
							H	4.37	4.10
							N	3.40	3.00
14a	H	$N(CH_3)_2$	–	$C_{20}H_{20}N_2O_5$ (368)	142	50	C	65.23	65.70
							H	5.43	5.60
							N	7.61	7.60
14b	H		–	$C_{22}H_{22}N_2O_6$ (410)	154	65	C	64.39	64.50
							H	5.37	5.50
							N	6.83	7.10

(*continued on next page*)

Table 5 (*continued*)

No.	R^1	R^2	Ar	Molecular formula (mol. wt.)	Melting point (°C)	Yield (%)	Microanalysis		
							Calculated (%)		Found (%)
14c	H		–	$C_{23}H_{24}N_2O_5$ (408)	138	60	C H N	67.65 5.88 6.86	67.40 5.50 6.83
14d	H		–	$C_{23}H_{25}N_3O_5$ (423)	160	65	C H N	65.25 5.91 9.93	65.30 5.40 10.10
14e	OCH_3	$N(CH_3)_2$	–	$C_{21}H_{22}N_2O_6$ (391)	120	50	C H N	63.32 5.73 7.04	63.00 5.20 7.46
14f	OCH_3		–	$C_{23}H_{24}N_2O_7$ (440)	170	65	C H N	62.77 5.45 6.36	62.40 5.20 5.72
14g	OCH_3		–	$C_{24}H_{26}N_2O_6$ (438)	98	55	C H N	65.75 5.94 6.39	65.60 5.60 5.80
15a	H	$N(CH_3)_2$	–	$C_{20}H_{10}N_2O_4$ (350)	168	50	C H N	68.57 5.14 8.00	69.00 5.00 8.30
15b	H		–	$C_{22}H_{20}N_2O_5$ (392)	174	65	C H N	67.35 5.10 7.14	67.50 4.00 7.20
15c	H		–	$C_{23}H_{22}N_2O_4$ (390)	190	60	C H N	70.77 5.64 7.18	70.86 6.17 7.50
15d	H		–	$C_{23}H_{23}N_3O_4$ (405)	180	60	C H N	68.15 5.68 10.37	68.50 4.90 10.20
15e	OCH_3	$N(CH_3)_2$	–	$C_{21}H_{20}N_2O_5$ (380)	155	55	C H N	66.32 5.26 7.37	66.10 5.00 7.30
15f	OCH_3		–	$C_{23}H_{22}N_2O_6$ (422)	185	65	C H N	65.40 5.21 6.64	65.00 5.70 6.52
15g	OCH_3		–	$C_{24}H_{24}N_2O_5$ (420)	138	60	C H N	68.57 5.71 6.67	68.20 5.30 6.36
17	–		–	$C_{23}H_{23}NO_6$ (409)	300	50	C H N	67.48 5.62 3.42	67.32 6.00 3.90
18	–	–	–	$C_{23}H_{21}NO_5$ (391)	246	65	C H N	70.59 5.37 3.58	70.89 5.12 3.53

4.1.9. 4-Methoxy-6-morpholinomethyl-7-phenyl-5H-furo[3,2-g]-[1]benzopyran-5-one ***18*** *(Scheme 4, Tables 5–7)*

Use a solution of **16** (1.0 g) in 20% H_2SO_4 (30 ml) and proceed exactly as above to prepare compounds **5a**, **b**. The separated solid was crystallized using ethanol. MS for **18** *m/z* 392 ($M^+ + 1$).

4.2. Pharmacology

Induction of gastric ulcer: Animals were individually housed in cages with wide mesh wire bottoms to prevent coprophagy. They were deprived of food for 36 h but allowed free access to water except for the last hour before the experiment. Gastric ulcer was induced by oral administration of 1 ml of 70% ethanol [18,19].

Assessment of gross mucosal damage: Rats were killed by cervical dislocation 1 h after ethanol administration. The abdominal cavity was opened and the stomach was excised, opened along the greater curvature, rinsed with saline and pinned flat on a cardboard to be exposed to gross lesions' evaluation [20].

Table 6
IR (KBr, cm^{-1}) spectra of the new synthesized compounds

Compound	IR (cm^{-1})
4a	3400 (OH), 1720, 1620 (2 C=O)
4b	3400 (OH), 1700, 1620 (2 C=O)
5a	1620 (C=O)
5b	1620 (C=O)
8	3400 (OH), 1660 (C=O)
9a	3350 (OH), 1660 (C=O)
9b	3400 (OH), 1640 (C=O)
9c	3400 (OH), 1660 (C=O)
11a	1640 (C=O)
11b	1660 (C=O)
11c	1640 (C=O)
11d	1640 (C=O)
11e	1620 (C=O)
12a	3350 (OH), 1640 (C=O)
12b	3400 (OH), 1660 (C=O)
13a	3400 (OH), 1640 (C=O)
13b	3350 (OH), 1640 (C=O)
14a	3300 (OH), 1720, 1620 (2 C=O)
14b	3400 (OH), 1720, 1660 (2 C=O)
14c	3400 (OH), 1750, 1620 (2 C=O)
14e	3400 (OH), 1740, 1620 (2 C=O)
14f	3300 (OH), 1750, 1635 (2 C=O)
14g	3350 (OH), 1740, 1640 (2 C=O)
15a	1620 (C=O)
15b	1640 (C=O)
15c	1620 (C=O)
15d	1640 (C=O)
15e	1620 (C=O)
15f	1640 (C=O)
16	3400 (OH), 1740, 1640 (2 C=O)
17	3400 (OH), 1740, 1620 (2 C=O)
18	1650 (C=O)

4.2.1. Determination of ulcer number

The gastric mucosal layer was carefully inspected for the occurrence of ulcers and their numbers were counted with the aid of an illuminated magnifying lens [21].

4.2.2. Determination of ulcer index

The length (in millimeters) of individual lesions in the mucosa was measured using Vernier caliper and the sum of lengths of all lesions in each stomach was regarded as the ulcer index [22].

4.2.3. Determination of preventive index

The preventive index (PI) of each drug is the percentage inhibition of gastric mucosal damage produced by such drug. It was calculated according to the following formula:

$$\mathrm{PI} = 100 - \frac{\text{Ulcer index of treated group}}{\text{Ulcer index of control group}} \times 100$$

Each rat was housed singly and fasted for 36 h. Test compounds were suspended in 1% Tween 80 and administered by i.p. injection (20 mg/kg) to the appropriate groups while

Table 7
^{1}H NMR spectra of the new synthesized compounds

Compound	^{1}H NMR δ (ppm)
4a	DMSO-d_6, D_2O: 2.20–2.62 (m, 4H, $(CH_2)_2N$), 3.39–3.96 (m, 6H, $(CH_2)_2O$ and CH_2N), 4.16 (s, 3H, OCH_3), 4.38 (s, 2H, $COCH_2CO$), 6.80 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.76 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.20 (t, 1H, pyridinyl H5), 8.80 (d, 1H, pyridinyl H4, *J*: 7.8 Hz), 9.00 (d, 1H, pyridinyl H6, *J*: 4.8 Hz), 9.40 (s, 1H, pyridinyl H2), 13.00 (s, 1H, OH exch.)
4b	$CDCl_3$–D_2O: 2.47–2.84 (m, 8H, $(CH_2)_4N$), 3.59 (s, 3H, NCH_3), 3.95 (s, 2H, CH_2), 4.12 (s, 3H, OCH_3), 4.78 (s, 2H, $COCH_2CO$), 6.84 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.42 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.20 (t, 1H, pyridinyl H5), 8.61 (d, 1H, pyridinyl H4, *J*: 7.6 Hz), 8.75 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.17 (s, 1H, pyridinyl H2), 13.26 (s, 1H, OH exch.)
5a	$CDCl_3$–D_2O: 2.40–2.96 (broad, 4H, $(CH_2)_2N$), 3.50 (m, 4H, $(CH_2)_2O$), 3.80 (s, 2H, CH_2), 4.10 (s, 3H, OCH_3), 6.81 (broad, 2H, γ-pyrone H and furan C*H*=CHO), 7.62 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.10 (t, 1H, pyridinyl H5), 8.64 (d, 1H, pyridinyl H4, *J*: 8.0 Hz), 8.76 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.23 (s, 1H, pyridinyl H2)
5b	DMSO-d_6, D_2O: 2.20–2.68 (m, 8H, $(CH_2)_4N$), 3.17 (s, 3H, NCH_3), 3.49 (s, 2H, CH_2), 4.08 (s, 3H, OCH_3), 6.90–7.10 (broad, 2H, γ-pyrone H and furan C*H*=CHO), 7.94 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.20–9.40 (m, 4H, pyridinyl H)
8	DMSO-d_6, D_2O: 7.12 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.22 (s, 1H, γ-pyrone H), 7.58 (s, 1H, ArH), 7.68 (m, 1H, pyridinyl H5), 8.00 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.54 (d, 1H, pyridinyl H4, *J*: 8 Hz), 8.85 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.33 (s, 1H, pyridinyl H2), 13.59 (s, 1H, OH exch.)
9a	DMSO-d_6, D_2O: 2.17–2.43 (broad, 4H, $(CH_2)_2N$), 3.32–3.90 (broad, 6H, $(CH_2)_2O$ and CH_2N), 7.04 (s, 1H, γ-pyrone H), 7.20 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.50 (t, 1H, pyridinyl H5), 7.90 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.20 (d, 1H, pyridinyl H4, *J*: 7 Hz), 8.69 (d, 1H, pyridinyl H6, *J*: 5.0 Hz), 9.40 (s, 1H, pyridinyl H2), 13.58 (s, 1H, OH exch.)
9c	DMSO-d_6, D_2O: 2.90–3.43 (broad, 10H, $(CH_2)_5N$), 3.85 (s, 2H, CH_2N), 6.96 (s, 1H, γ-pyrone H), 7.20 (d, 1H, furan C*H*=CHO, *J*: 1.8 Hz), 7.63 (t, 1H, pyridinyl H5), 7.90 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.45 (d, 1H, pyridinyl H6, *J*: 7.7 Hz), 8.78 (d, 1H, pyridinyl H6, *J*: 4 Hz), 9.26 (s, 1H, pyridinyl H2), 13.50 (s, 1H, OH exch.)
11a	DMSO-d_6, D_2O: 4.09 (s, 3H, OCH_3), 6.82 (s, 2H, γ -pyrone and ArH), 7.28 (d, 1H, furan C*H*=CHO, *J*: 1.8 Hz), 7.56 (m, 2H, ArH), 7.72 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.09 (m, 3H, ArH)
11b	DMSO-d_6, D_2O: 4.08 (s, 3H, OCH_3), 6.83 (s, 2H, γ-pyrone and ArH), 7.27 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.59 (d, 2H, ArH, *J*: 8.8 Hz), 7.68 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.09 (d, 2H, ArH, *J*: 8.7 Hz)
11c	DMSO-d_6, D_2O: 3.84 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.71 (s, 2H, γ-pyrone and ArH), 7.08 (d, 2H, ArH, *J*: 9 Hz), 7.27 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.69 (d, 1H, furan CH=C*H*O, *J*: 1.8 Hz), 8.05 (d, 2H, ArH, *J*: 8.7 Hz)
11d	DMSO-d_6, D_2O: 2.40–2.60 (broad, 4H, $(CH_2)_2N$), 3.10–3.60 (broad, 4H, $(CH_2)_2O$), 3.74 (s, 2H, CH_2N), 4.13 (s, 3H, OCH_3), 6.80–8.00 (broad, 8H, γ-pyrone, furan H and ArH)
11e	$CDCl_3$–D_2O: 3.20 (broad, 4H, $(CH_2)_2N$), 3.80–4.00 (broad, 6H, $(CH_2)_2O$ and CH_2N), 4.27 (s, 3H, OCH_3), 6.67 (s, 1H, γ-pyrone H), 7.14 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.49 (d, 2H, ArH, *J*: 8.0 Hz), 7.69 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 7.89 (d, 2H, ArH, *J*: 8.0 Hz)

(*continued on next page*)

Table 7 (*continued*)

Compound	^{1}H NMR δ (ppm)
12a	DMSO-d_6, D_2O: 7.04 (s, 1H, γ-pyrone H), 7.13 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.48 (s, 1H, ArH), 7.58–7.62 (m, 5H, ArH), 8.09 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 13.67 (s, 1H, OH exch.)
12b	DMSO-d_6, D_2O: 7.06 (s, 1H, γ-pyrone H), 7.40 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.61 (d, 2H, ArH, *J*: 7 Hz), 8.02 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.12 (d, 2H, ArH, *J*: 7 Hz), 13.60 (s, 1H, OH exch.)
13a	DMSO-d_6, D_2O: 2.30–2.43 (m, 4H, $(CH_2)_2N$), 3.20–3.80 (m, 6H, $(CH_2)_2O$ and CH_2N), 7.03 (s, 1H, γ-pyrone H), 7.19 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.60–8.11 (broad, 6H, ArH and furan CH=C*H*O), 13.50 (s, 1H, OH exch.)
13b	DMSO-d_6, D_2O: 3.20 (broad, 4H, $(CH_2)_2N$), 3.55 (broad, 4H, $(CH_2)_2O$), 4.02 (s, 2H, CH_2N), 6.96 (s, 1H, γ-pyrone H), 7.04 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.64 (d, 2H, ArH, *J*: 7.4 Hz), 8.00 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.17 (d, 2H, ArH, *J*: 7.8 Hz), 13.65 (s, 1H, OH exch.)
14a	DMSO-d_6, D_2O: 3.36 (s, 6H, $N(CH_3)_2$), 3.82 (d, 2H, CH_2N), 4.05 (s, 3H, OCH_3), 7.29 (s, 1H, ArH), 7.36–7.48 (m, 2H, furan C*H*=CHO and COCHCO), 7.93–8.05 (broad, 3H, furan CH=C*H*O, pyridinyl H4 and pyridinyl H5), 8.58 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 8.79 (s, 1H, pyridinyl H2), 13.00 (s, 1H, OH exch.)
14b	DMSO-d_6, D_2O: 2.20–2.60 (broad, 4H, $(CH_2)_2N$), 3.17–3.89 (broad, 6H, $(CH_2)_2O$ and CH_2N), 4.11 (s, 3H, OCH_3), 6.97 (s, 1H, ArH), 7.20 (t, 1H, COCHCO), 7.31 (d, 1H, furan C*H*=CHO, *J*: 1.8 Hz), 7.80 (d, 1H, furan CH=C*H*O, *J*: 1.8 Hz), 8.08 (t, 1H, pyridinyl H5), 8.30 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.50 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.30 (s, 1H, pyridinyl H2), 13.20 (s, 1H, OH exch.)
14c	DMSO-d_6, D_2O: 2.90–3.99 (broad, 12H, $(CH_2)_5$ N and CH_2N), 4.11 (s, 3H, OCH_3), 6.70 (s, 1H, ArH), 6.90 (t, 1H, COCHCO), 7.20 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.70 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 7.90(t, 1H, pyridinyl H5), 8.30 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.80 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.01 (s, 1H, pyridinyl H2), 13.00 (s, 1H, OH exch.)
14e	DMSO-d_6, D_2O: 2.30–2.60 (broad, 4H, $(CH_2)_2N$), 3.10–3.60 (broad, 6H, $(CH_2)_2O$ and CH_2N), 3.95 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 7.23 (t, 1H, COCHCO), 7.30 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.70 (d, 1H, furan CH=C*H*O, *J*: 1.8 Hz), 8.12 (t, 1H, pyridinyl H5), 8.40 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.50 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.10 (s, 1H, pyridinyl H2), 13.10 (s, 1H, OH exch.)
14f	$CDCl_3$ –D_2O: 2.04–2.88 (broad, 10H, $(CH_2)_5N$), 3.48 (d, 2H, CH_2N, *J*: 7 Hz), 3.99 (s, 3H, OCH_3), 4.28 (s, 3H, OCH_3), 6.92 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.49 (t, 1H, COCHCO), 7.85 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.22 (d, 1H, pyridinyl H4, *J*: 7.6 Hz), 8.52–8.93 (m, 2H, pyridinyl H5 and pyridinyl H6), 9.36 (s, 1H, pyridinyl H2), 13.06 (s, 1H, OH exch.)
14g	DMSO-d_6, D_2O: 2.96 (s, 3H, NCH_3), 3.10–3.70 (broad, 10H, $(CH_2)_4N$ and CH_2N), 3.92 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.10 (t, 1H, COCHCO), 7.30 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.60 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.20 (t, 1H, pyridinyl H5), 8.40 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.70 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.20 (s, 1H, pyridinyl H2), 12.80 (s, 1H, OH exch.)
15a	DMSO-d_6, D_2O: 3.41–3.45 (s, 6H, $N(CH_3)_2$), 4.05 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2N), 7.00 (s, 1H, ArH), 7.29 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.51 (m, 1H, pyridinyl H5), 8.00 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.12 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.60 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 8.79 (s, 1H, pyridinyl H2)

Table 7 (*continued*)

Compound	^{1}H NMR δ (ppm)
15b	DMSO-d_6, D_2O: 2.08–2.60 (broad, 4H, $(CH_2)_2N$), 3.20–3.80 (broad, 6H, $(CH_2)_2O$ and CH_2N), 4.09 (s, 3H, OCH_3), 7.10 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.25 (s, 1H, ArH), 7.80 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.00 (t, 1H, pyridinyl H5), 8.60 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.80 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.40 (s, 1H, pyridinyl H2)
15c	DMSO-d_6, D_2O: 2.00–2.90 (broad, 10H, $(CH_2)_5$ N), 3.90 (s, 2H, CH_2N), 4.13 (s, 3H, OCH_3), 7.08 (s, 1H, ArH), 7.33 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.80 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.10 (t, 1H, pyridinyl H5), 8.30 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.70 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.30 (s, 1H, pyridinyl H2)
15d	DMSO-d_6, D_2O: 2.00–2.80 (broad, 8H, $(CH_2)_4N$), 3.16 (s, 3H, NCH_3), 3.92 (s, 2H, CH_2N), 4.20 (s, 3H, OCH_3), 6.90 (s, 1H, ArH), 7.15 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.90 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.10 (t, 1H, pyridinyl H5), 8.30 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.70 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.20 (s, 1H, pyridinyl H2)
15e	DMSO-d_6, D_2O: 2.30–2.70 (broad, 4H, $(CH_2)_2N$), 3.20–3.50 (broad, 4H, $(CH_2)_2O$), 3.88 (s, 2H, CH_2N), 4.05 (s, 3H, OCH_3), 4.23 (s, 3H, OCH_3), 7.20 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.80 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.13 (t, 1H, pyridinyl H5), 8.50 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.80 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.20 (s, 1H, pyridinyl H2)
15f	DMSO-d_6, D_2O: 2.20–2.85 (m, 10H, $(CH_2)_5N$), 3.80 (s, 2H, CH_2N), 3.97 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 7.08 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.92 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 8.13 (t, 1H, pyridinyl H5), 8.59 (d, 1H, pyridinyl H4, *J*: 7.5 Hz), 8.98 (d, 1H, pyridinyl H6, *J*: 4.5 Hz), 9.20 (s, 1H, pyridinyl H2)
17	DMSO-d_6, D_2O: 2.79 (broad, 4H, $(CH_2)_2N$), 3.15 (broad, 4H, $(CH_2)_2O$), 4.00 (s, 3H, OCH_3), 4.11 (d, 2H, CH_2N, *J*: 6.4 Hz), 6.98 (s, 1H, ArH), 7.20 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.46 (t, 1H, COCHCO), 7.69–7.77 (m, 5H, ArH), 8.05 (d, 1H, furan CH=C*H*O, *J*: 2 Hz), 12.75 (s, 1H, OH exch.)
18	DMSO-d_6, D_2O: 2.78 (broad, 4H, $(CH_2)_2N$), 3.07 (broad, 4H, $(CH_2)_2O$), 3.65 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2N), 7.25 (d, 1H, furan C*H*=CHO, *J*: 2 Hz), 7.47–7.69 (m, 6H, ArH), 8.03 (d, 1H, furan CH=C*H*O, *J*: 2 Hz)

control group received equivalent volume of 1% Tween 80. One-hour later gastric ulcer was induced in 36 h fasted animals by oral administration of 1 ml 70% ethanol in distilled water. Animals were sacrificed by cervical dislocation 1 h post ulcer induction and stomachs were dissected. In each stomach, ulcers were counted (Table 1) and the length of each lesion was measured using Vernier caliper, then the sum of lengths was calculated and served as ulcer index (Tables 2 and 3); the preventive index was calculated regarding the effect of drug on ulcer index (Table 4).

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