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Short communication

Synthesis and anti-inflammatory activity of 1-acetyl-5-substitute daryl-3-(β-aminonaphthyl)-2-pyrazolines and β-(substituted aminoethyl) amidonaphthalenes☆

Ekta Bansal†, V.K. Srivastava, Ashok Kumar*

Medicinal Chemistry Division, Department of Pharmacology, L.L.R.M. Medical College, Meerut 250004, U.P., India

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Abstract – The title compounds were prepared by reaction of β-acetylamino-naphthalene with different aromatic aldehydes followed by cyclisation with hydrazine hydrate and with different primary or secondary amines (Mannich's reaction), respectively. The structures of new compounds were confirmed by ^{1}H-NMR and IR spectral data. Anti-inflammatory and ulcerogenic activities in vivo were evaluated and compared with the standard drugs, phenylbutazone and indomethacin. Some compounds of the series exhibited promising anti-inflammatory activity with a lower ulcerogenic liability than the standard drugs. © 2001 Éditions scientifiques et médicales Elsevier SAS

Zusammenfassung – dkflsdhgkfdjz © 2000 Éditions scientifiques et médicales Elsevier SAS

chalcones / pyrazolines / substituted amidonaphthalene / anti-inflammatory activity / ulcerogenic activity / acute toxicity

1. Introduction

Naphthalene, an aromatic nucleus has gained prominence after the discovery of naproxen [1] and nabumetone [2] which are currently useful drugs for the treatment of various inflammatory disorders. Heterocyclic/aliphatic functionalised systematic variation at β-position of naphthalene nucleus remarkably increase the anti-inflammatory activity [3–5]. Pyrazolines are also well known for their pronounced anti-inflammatory activity [6–10]. In view of these observations, it was thought worthwhile to synthesise some new β-substituted naphthylpyrazolines and β-substituted amidonaphthalenes to evaluate them for their anti-inflammatory activity.

2. Chemistry

The synthetic routes of compounds are outlined in *figure 1*. Compound (**1**), i.e. β-acetylaminonaphthalene was prepared by reacting β-aminonaphthalene with acetylchloride in benzene. Compound (**1**) on refluxing with various aromatic aldehydes for 10 h in the presence of 2 % NaOH yielded β-aminonaphthyl substituted chalcones (**2a**–**2e**) which on cyclisation with 90 % hydrazine hydrate in the presence of few drops of glacial acetic acid afforded 1-acetyl-5-substituted aryl-3-(β-aminonaphthyl)-2-pyrazolines (**3a**–**3e**) [11]. On the other side, compound **1** underwent Mannich's reaction (i.e. reaction of compound **1** with various primary or secondary amines in the presence of formaldehyde) to yield β-(substituted aminoethyl) amidonaphthalenes (**2a′**–**2t′**).

3. Pharmacological results and discussion

All new compounds were tested in vivo in order to evaluate their pharmacological activity.

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* Correspondence and reprints.

† Part of Ph.D. Thesis.

The anti-inflammatory effects of all the compounds of this series have been reported in *tables I and II*.

The characteristic feature of route (**1**) of this series is the presence of substituted alkyl chain at amino group of β-aminonaphthalene and their conversion into five-membered ring structure. All the compounds (**2a**–**2e** and **3a**–**3e**) exhibited more or less anti-inflammatory activity. It was observed that compound having furyl group (compound **2b**) as substituent showed the least activity (17.97 %) while compound substituted with phenyl ring having methoxy group at either *ortho* or *para* positions exhibited the maximum percent inhibition of oedema. However, *ortho* compound (**2d**) showed more activity (39.32 %) than the corresponding *para* compound (**2c**) (33.70 %). Compounds having phenyl group as substituent (**2a**) showed 24.72 % activity and the compound substituted with phenyl group having dimethylamino group at *p*-position exhibited 29.21 % inhibition. Cyclisation of chalcones into pyrazolines in general, enhanced the activity. Compounds **3c** and **3d** exhibited more potent activity than that of phenylbutazone but less activity than indomethacin, the reference drugs.

Hence it may be concluded that substitution with phenyl moiety having methoxy group either at *ortho* or *para* position enhances the activity. Of the two (*o* and *p*), *o*-isomer is more active. *Figure 2* shows the anti-inflammatory activity of compound **3d** and phenylbutazone at three different doses (25, 50 and 100 mg kg^{-1} per oral). Further, compound **3d** exhibited less ulcerogenic potentiality as compared with phenylbutazone (UD_{50} of **3d** = 132.9 mg kg^{-1} i.p. and UD_{50} of phenylbutazone = 66.6 mg kg^{-1} i.p.). Ulcerogenic potentiality of the compounds (oral administration) is given in the *table III*.

On the other side of series (route 2), almost all the compounds showed potent anti-inflammatory activity. However, some compounds have shown more potent activity than phenylbutazone (but less than indomethacin) such as, compound **2d′**, in which phenyl ring, having an electronegative atom, i.e. 'Cl' at *m*-position, is present as substituent; compound **2n′**, in which phenyl moiety is having an acidic group and an electronegative atom, i.e. 'Br' at *p*-position; compound **2o′**, in which an acidic group is attached to the phenyl moiety and two Br atoms at *ortho* and

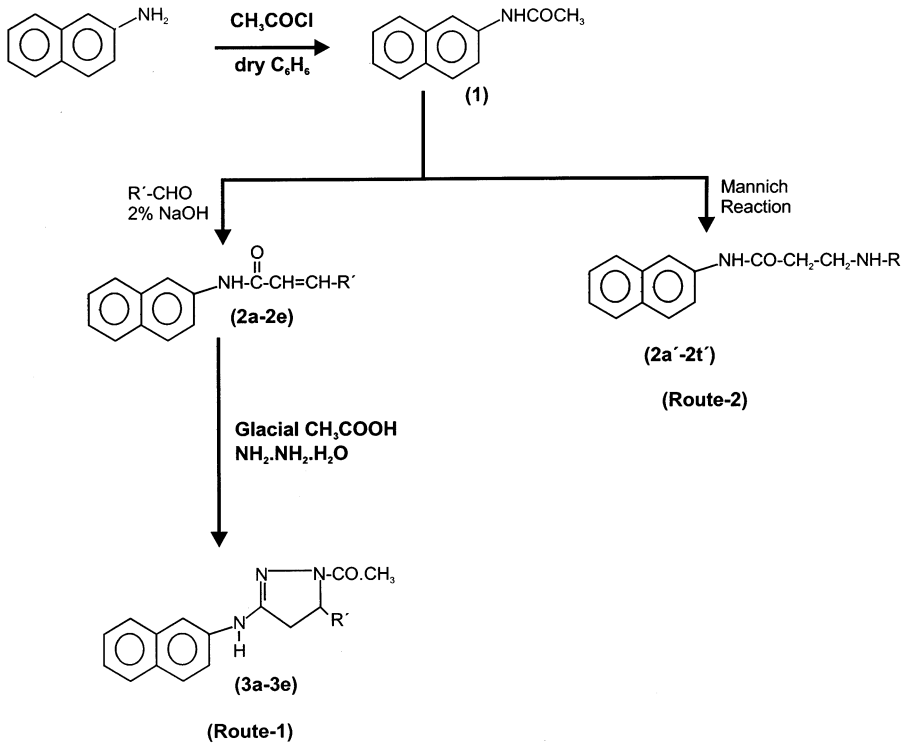
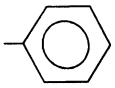
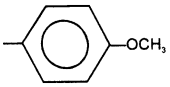
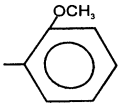
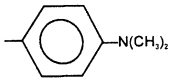
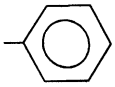
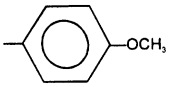
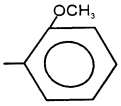
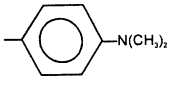


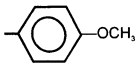
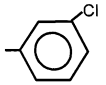
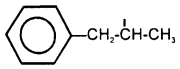
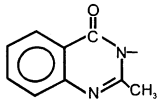
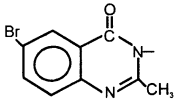
Figure 1.

Table I. Characterisation data and anti-inflammatory activity of compounds (**2a**–**2e** and **3a**–**3e**).

Compound number	**R′**	m.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Anti-inflammatory activity [b] (% inhibition)	ALD_{50} (mg kg^{-1} p.o.; maximum dose tested)
1	–	122	90	ethanol–water	$C_{12}H_{11}NO$	185	–	–
2a		138	70	DMF	$C_{19}H_{15}NO$	273	24.72	>800
2b		126	65	acetone	$C_{17}H_{13}NO_2$	263	17.97	>800
2c		134	60	methanol–water	$C_{20}H_{17}NO_2$	303	33.70 [c]	>1600
2d		144	65	methanol	$C_{20}H_{17}NO_2$	303	39.32 [c]	>1600
2e		152	70	acetic acid–water	$C_{21}H_{20}N_2O$	316	29.21 [c]	>1000
3a		126	50	ethanol	$C_{21}H_{19}N_3O$	329	35.71	>1600
3b		118	40	acetone –pet.ether	$C_{19}H_{17}N_3O_2$	319	23.21	>800
3c		112	45	acetone–benzene	$C_{22}H_{21}N_3O_2$	359	42.85 [c]	>1600
3d		136	40	ethanol	$C_{22}H_{21}N_3O_2$	359	46.43 51.78 [c] 67.85	>1600
3e		142	35	DMF	$C_{23}H_{24}N_4O$	372	37.50 [c]	>1600

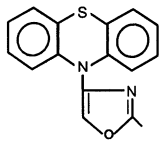
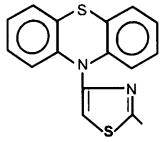
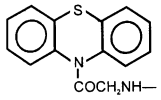
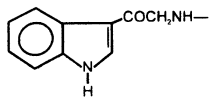
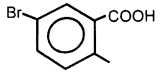
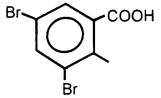
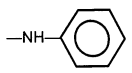
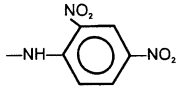
[a] C, H, N were found within ± 0.4 %.
[b] All compounds were tested at a dose of 50 mg kg^{-1} p.o. except **3d** which was tested at 25, 50 and 100 mg kg^{-1} p.o.
[c] $P < 0.001$.

Table II. Characterisation data and anti-inflammatory activity of compounds (**2a′**–**2t′**).

Compound number	R′	m.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Dose (mg kg^{-1} p.o.)	Anti-inflammatory activity (% inhibition)	ALD_{50} (mg kg^{-1} p.o.; maximum dose tested)
2a′		192	35	toluene–pet.ether	$C_{19}H_{18}N_2O$	290	50	19.69	>800
2b′		134	50	ethanol	$C_{20}H_{20}N_2O_2$	320	50	34.85 [b]	>1600
2c′		168	40	THF	$C_{20}H_{20}N_2O_2$	320	50	39.39 [b]	>1600
2d′		138	25	hexane–toluene	$C_{19}H_{17}N_2OCl$	324.5	25 50 100	39.39 57.57 [b] 72.72	>1600
2e′		240	35	DMF	$C_{19}H_{17}N_2OCl$	324.5	50	40.90 [b]	>1600
2f′		102	20	acetone	$C_{22}H_{24}N_2O$	332	50	21.21	>800
2g′		146	40	methanol	$C_{22}H_{20}N_4O_2$	372	50	28.78	>800
2h′		112	55	ethanol–water	$C_{22}H_{19}N_4O_2Br$	451	50	30.30	>1000

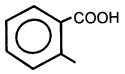
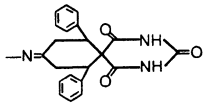
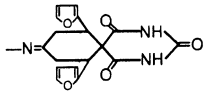
(continued)

Table II. (Continued)

Compound number	R′	m.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Dose (mg kg^{-1} p.o.)	Anti-inflammatory activity (% inhibition)	ALD_{50} (mg kg^{-1} p.o.; maximum dose tested)
2i′		136	35	acetone	$C_{28}H_{22}N_4O_2S$	478	50	21.21	>800
2j′		90	50	acetic acid–water	$C_{28}H_{22}N_4OS_2$	494	50	24.24	>800
2k′		174	20	toluene	$C_{27}H_{24}N_4O_2S$	468	50	22.72	>800
2l′		332	50	benzene–pet.ether	$C_{23}H_{22}N_4O_2$	386	50	36.54 [b]	>1600
2m′	–OH.HCl	138	40	hexane	$C_{13}H_{15}N_2O_2Cl$	266.5	50	13.46	>800
2n′		158	25	DMF	$C_{20}H_{17}N_2O_3Br$	413	50	40.38 [b]	>1600
2o′		174	45	methanol	$C_{20}H_{16}N_2O_3Br_2$	492	25 50 100	44.23 59.61 [b] 67.30	>1600
2p′		132	35	benzene	$C_{19}H_{19}N_3O$	305	50	32.69 [b]	>1000
2q′		110	30	THF	$C_{19}H_{17}N_5O_5$	395	50	42.30 [b]	>1600

(continued)

Table II. (Continued)

Compound number	R′	m.p. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Dose (mg kg^{-1} p.o.)	Anti-inflammatory activity (% inhibition)	ALD_{50} (mg kg^{-1} p.o.; maximum dose tested)
2r′		152	40	ethanol–water	$C_{20}H_{18}N_2O_3$	334	50	38.46 [b]	>1600
2s′		124	45	toluene	$C_{34}H_{31}N_5O_4$	569	50	22.72	>800
2t′		137	35	acetone	$C_{30}H_{27}N_5O_6$	549	50	19.69	>800
Phenyl butazone							25 50 100	15.0 38.9 65.2	
Indomethacin							1.8 3.6 5.4	38.30 49.40 63.00	

[a] C, H, N were found within ± 0.4 %.
[b] $P < 0.001$.

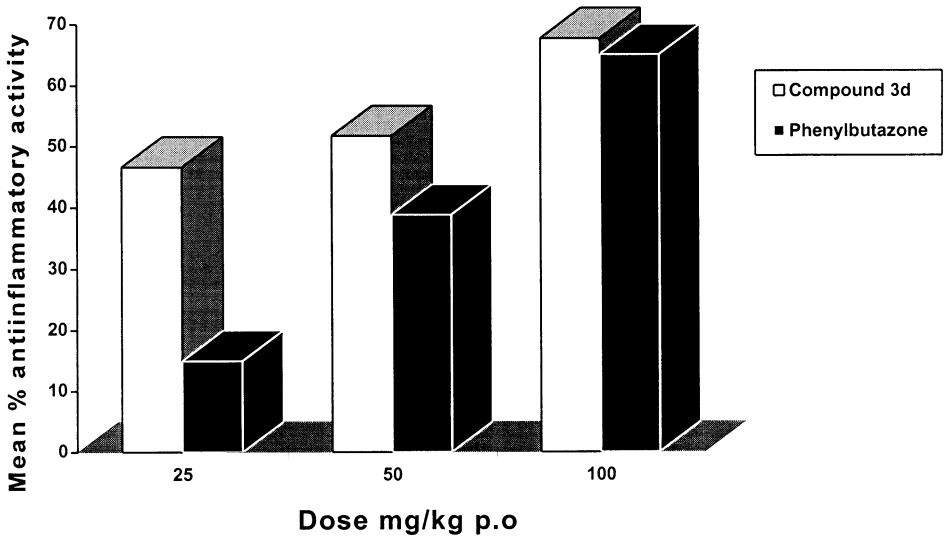


Figure 2. The bar diagram showing mean % anti-inflammatory activity of compound **3d** and Phenylbutazone at three graded doses.

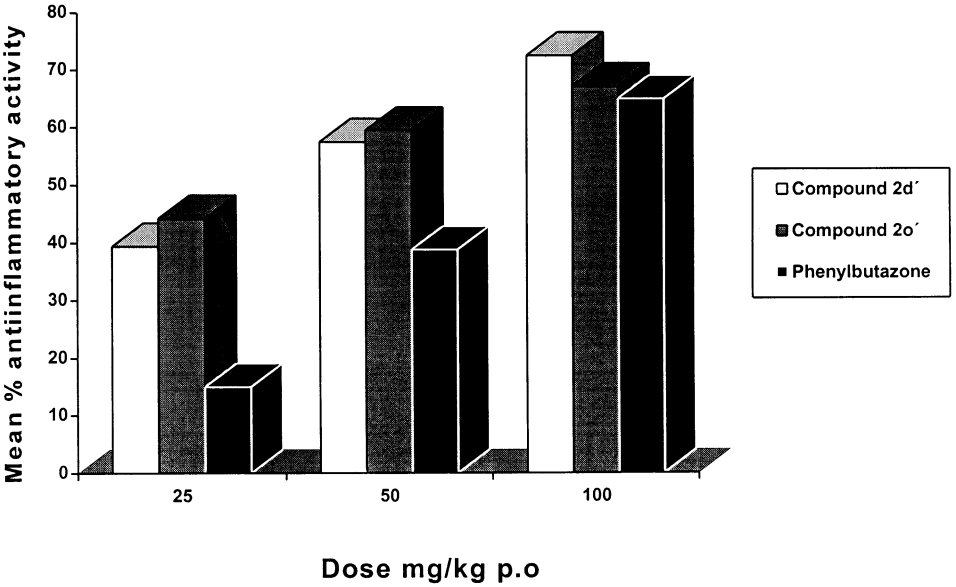


Figure 3. The bar diagram showing mean % anti-inflammatory activity of compounds **2d′, 2o′** and Phenylbutazone at three graded doses.

para position of phenyl ring are present; compound **2q′** in which two NO_2 groups at *ortho* and *para* position are attached to the phenyl ring. These compounds (**2d′**, **2n′**, **2o′**, **2q′**) exhibited (57.57, 40.38, 59.61 and 42.30 %, respectively) inhibition of oedema in rat paw.

Therefore, it may be concluded that when the compound is substituted with a phenyl moiety having an electronegative atom at *ortho* or *para* position or having some acidic group in the ring or $-NO_2$ group, then it shows promising anti-inflammatory activity.

Figure 3 shows the anti-inflammatory activity of compounds **2d′**, **2o′** and the reference drug phenylbutazone at three graded doses (25, 50 and 100 mg kg^{-1} per oral).

Table III. Ulcerogenic liability of compounds **3d**, **2d′**, **2n′**, **2o′**, **2p′**, **2r′**, phenylbutazone and indomethacin.

Serial number	Compound	Dose (mg kg^{-1} p.o)	Ulcerogenic liability incidence (%)
1	Indomethacin	1.8	60
		3.6	80
		5.4	100
		25	30
2	Phenylbutazone	50	50
		100	60
		25	20
3	**3d**	50	30
		100	50
		25	20
4	**2d′**	50	20
		100	50
		25	50
5	**2n′**	50	70
		100	90
		25	30
6	**2o′**	50	40
		100	60
		25	60
7	**2p′**	50	60
		100	90
		25	40
8	**2r′**	50	60
		100	80

Considering ulcerogenic liabilities of potent compounds, compound **2d′** was found to possess less ulcerogenic potentiality as compared with phenylbutazone whereas compound **2o′** possessed nearly the same ulcerogenic liability as phenylbutazone (UD_{50} of **2d′** = 182.5 mg kg^{-1} i.p., UD_{50} of **2o′** = 69.18 mg kg^{-1} i.p. and UD_{50} of phenylbutazone = 66.6 mg kg^{-1} i.p.). Considering oral administration of the compounds and the reference drugs, compounds **3d** (the most active pyrazoline), **2d′** and **2o′** are found to be safer than phenyl butazone and indomethacin with respect to ulcerogenic liability while the acidic compounds (**2n′**, **2p′** and **2r′**) showed more percent incidence than phenylbutazone but less percent incidence (or equipotency) than indomethacin. Ulcerogenic potentiality (p.o.) is given in *table IV*.

4. Experimental protocols

4.1. Chemistry

The melting points are uncorrected. Carbon and hydrogen analysis were performed on CHN analyses, Carlo Erba 1108, Heracus, at the Central Drug Research Institute (Lucknow). Analysis (C, H, N) were within ±0.4 % of the theoretical values. The IR spectra were recorded on Backman-Acculab-10 spectrophotometer (ν_{max} in cm^{-1}). The ^{1}H-NMR spectra were recorded in $CDCl_3$ on Brucker 400-FT instrument, Mass spectra were determined on JEOL-JMS-D-300 spectrometer. Silica gel-G plates were used for TLC, the eluent was a mixture of methanol–benzene in 2:8 proportion.

*4.1.1. β-Acetylaminonaphthalene (**1**)*

To a solution of β-aminonaphthalene (0.01 mol) in dry benzene (50 mL), acetylchloride (0.01 mol) was added drop by drop at 0–5 °C. The reaction mixture was stirred for 1 h and kept overnight. The reaction mixture was distilled off and then poured onto ice. The solid thus obtained was recrystallised from ethanol–water. Physical, analytical and spectroscopic data are given in *tables I and IV*, respectively.

*4.1.2. β-Aminonaphthyl-substituted chalcones (**2a**–**2e**)*

A solution of β-acetylamino naphthalene (0.01 mol) in absolute ethanol (50 mL) is refluxed with various aromatic aldehydes in the presence of 2 % NaOH for 10 h, concentrated, cooled and poured onto ice. The solids thus obtained were recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compounds (**2a**–**2e**) are given in *tables I and III*, respectively.

*4.1.3. 1-Acetyl-5-substituted aryl-3-(β-aminonaphthyl)-2-pyrazolines (**3a**–**3e**)*

To a solution of compound (**2a**–**2e**) (0.02 mol) in ethanol, 99 % hydrazine hydrate (0.04 mol) and few drops of glacial acetic acid were added. The reaction mixtures were refluxed for 8–10 h, distilled in vacuum and cooled. The separated solids were filtered, washed with ether and recrystallised from appropriate solvents. Physical, analytical and spectroscopic data of compounds (**3a**–**3e**) are given in *tables I and IV*, respectively.

*4.1.4. β-(Substituted aminoethyl) amidonaphthalenes (**2a′**–**2t′**)*

To a solution of β-acetylaminonaphthalene (0.01 mol)

Table IV. Spectral data of compounds (**2a**–**2e**), (**3a**–**3e**) and (**2a′**–**2t′**).

Compound	$[M]^+$ m/z	^{1}H-NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
2a	273	5.80 (ss, 1H, N–*H*), 6.75 (d, 1H, –CO–C*H*=) 8.25–7.60 (m, 12H, Ar–*H*), 8.60 (d, 1H,=C*H*–Ar)	1720 (C=O), 1620 (CH=CH), 3410 (NH), 1580 (C⋯C of aromatic ring)
2b	263	5.85 (ss, 1H, N*H*), 6.70 (d, 1H, –CO–C*H*=) 8.65(d, 1H, =C*H*–Ar), 8.30–7.75 (m, 10H, Ar–*H*)	1750 (C=O), 1630 (CH=CH), 3400 (NH), 1580 (C⋯C of aromatic ring), 1070 (C–O–C)
2c	303	5.75 (ss, 1H, N*H*), 6.80 (d, 1H, –CO–C*H*=) 8.65 (d, 1H, =C*H*–Ar), 8.20–7.65 (m, 11H, Ar–*H*), 3.70N (s, 3H, Ar–COCH_3)	1710 (C=O), 1640 (CH=CH), 3420 (NH), 1550 (C⋯C of aromatic ring)
2d	303	3.80 (s, 3H, Ar–OCH_3), 8.20–7.60 (m, 11H, Ar–*H*) 5.85 (ss, 1H, N–H), 8.70 (d, 1H, =C*H*–Ar), 6.65 (d, 1H, –CO–C*H*=)	1730 (C=O), 1640 (CH=CH), 3410 (NH), 1560 (C⋯C of aromatic ring)
2e	316	5.80 (ss, 1H, N*H*), 6.60 (d, 1H, –CO–C*H*=), 8.70 (d, 1H, =C*H*–Ar), 8.25–7.60 (m, 11H, Ar–*H*), 1.5 [s, 6H, –N$(CH_3)_2$]	1730 (C=O), 1620 (CH=CH), 3420 (NH), 1550 (C⋯C of aromatic ring)
3a	329	2.60 (s, 3H, CO–CH_3), 7.65 (d, 2H, pyrazoline CH_2), 8.25–7.80 (m, 12H, Ar–*H*), 8.40 (t, 1H, –C*H*–Ar), 9.3 (s, 1H, N*H* exchangeable with D_2O)	3400 (N–H), 1530 (N–N), 1580 (C=N), 1510 (C–N), 1560 (C⋯C of aromatic ring), 1710 (C=O)
3b	319	2.65 (s, 3H, CO–CH_3), 7.60 (d, 2H, pyrazoline CH_2), 8.35–7.95 (m, 10H, Ar–*H*), 8.45 (t, 1H, –C*H*–Ar), 9.25 (s, 1H, N*H* exchangeable with D_2O)	3420 (N–H), 1520 (N–N), 1560 (C=N), 1530 (C–N), 1510 (C⋯C of aromatic ring), 1740 (C=O), 1060 (C–O–C)
3c	359	2.70 (s, 3H, CO–CH_3), 7.75 (d, 2H, pyrazoline CH_2), 8.15–7.60 (m, 11H, Ar–*H*), 8.30 (t, 1H, –C*H*–Ar), 9.25 (s, 1H, N*H* exchangeable with D_2O), 3.70 (s, 3H, Ar–OCH_3)	3400 (N–H), 1500 (N–N), 1580 (C=N), 1510 (C–N), 1560 (C⋯C of aromatic ring), 1720 (C=O)
3d	359	8.20–7.50 (m, 11H, Ar–H) 7.70 (d, 2H, pyrazoline CH_2), 8.30 (t, 1H, –C–Ar), 2.75 (s, 3H, CO–CH_3), 3.80 (s, 3H, OCH_3), 9.3 (s, 1H, N*H* exchangeable with D_2O)	1520 (N–N), 1590 (C=N), 1500 (C–N), 1750 (C=O), 1560 (C⋯C of aromatic ring), 3400 (NH)
3e	372	2.60 (s, 3H, CO–CH_3), 7.70 (d, 2H, pyrazoline CH_2), 8.20–7.60 (m, 11H, Ar–*H*), 8.35 (t, 1H, –C*H*–Ar), 9.20 (s, 1H, N*H* exchangeable with D_2O), 1.45 [s, 6H, –N$(CH_3)_2$]	3430 (N–H), 1520 (N–N), 1560 (C=N), 1500 (C–N), 1570 (C⋯C of aromatic ring), 1740 (C=O)
2a′	290	5.80 (s, 2H, –CO–N*H*–) 5.65 (hump, 1H–NH_2), 5.2–4.00 (m, 4H, CH_2–CH_2), 8.30–7.50 (m, 12H, Ar–*H*)	3400 (N–H), 3060 (aromatic C–H), 2970, 2860 (aliphatic C–H), 1510 (C⋯C of aromatic ring), 1680 (C=O) 1220 (C–N)
2b′	320	5.80 (s, 2H, –CO–N*H*–), 5.65 (hump, 1H–NH_2), 5.2–4.00 (m, 4H, CH_2–CH_2), 8.35–7.65 (m, 11H, Ar–*H*), 3.85 (s, 3H, Ar–OCH_3)	3410 (N–H), 3080 (aromatic C–H), 2960, 2850 (aliphatic C–H), 1500 (C⋯C of aromatic ring), 1670 (C=O) 1240 (C–N)
2c′	320	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.10 (m, 4H, CH_2–CH_2), 8.25–7.50 (m, 11H, Ar–*H*), 3.80 (s, 3H, Ar–OCH_3)	3400 (N–H), 3020 (aromatic C–H), 2950, 2890 (aliphatic C–H), 1580 (C⋯C of aromatic ring), 1680 (C=O) 1210 (C–N)
2d′	324	5.85 (s, 1H, –CO–N*H*), 5.60 (hump, 1H, –N*H*–CH_2), 5.20–4.00 (m, 4H, CH_2–CH_2), 8.30–7.60 (m, 11H, Ar–*H*)	3420 (N–H), 3040 (aromatic C–H), 2960, 2880 (aliphatic C–H), 1540 (C⋯C of aromatic ring), 1660 (C=O) 1230 (C–N), 680 (C–Cl)
2e′	324	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.30–7.60 (m, 11H, Ar–*H*)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C⋯C of aromatic ring), 1670 (C=O) 1210 (C–N), 680 (C–Cl)

(continued)

Table IV. (Continued)

Compound	$[M]^+$ m/z	^{1}H-NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
2f′	332	5.85 (s, 1H, –CO–N*H*), 5.75 (hump, 1H, –N*H*–CH_2), 5.40–4.00 (m, 4H, CH_2–CH_2), 8.30–7.70 (m, 12H, Ar–H), 2.50 (d, 2H, –CH_2), 1.30 (d, 3H, –CH_3), 1.8 (m, 1H, –CH)	3400 (N–H), 3060 (aromatic C–H), 2970, 2860 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N)
2g′	372	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.20–7.55 (m, 11H, Ar–H), 1.38 (s, 3H, –CH_3)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N), 1640 (C=N), 1750 (C=O of quinazolinone ring), 1310 (NCN)
2h′	451	5.85 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.25–4.00 (m, 4H, CH_2–CH_2), 8.20–7.50 (m, 11H, Ar–H), 1.38 (s, 3H, –CH_3)	3430 (N–H), 3060 (aromatic C–H), 2960, 2870 (aliphatic C–H), 1530 (C···C of aromatic ring), 1670 (C=O) 1220 (C–N), 1640 (C=N), 1750 (C=O of quinazolinone ring), 1330 (NCN)
2i′	478	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.35–7.20 (m, 16H, Ar–H)	3410 (N–H), 3040 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N), 1070 (C–O–C), 1140 (C–S)
2j′	494	5.80 (s, 1H, –CO–N*H*), 5.65 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.30–7.20 (m, 16H, Ar–H)	3420 (N–H), 3020 (aromatic C–H), 2970, 2850 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N), 1130 (C–S)
2k′	468	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.25–7.20 (m, 15H, Ar–H), 4.0 (d, 2H, –CH_2), 4.8 (t, 1H, $COCH_2NH$)	3400 (N–H), 3040 (aromatic C–H), 2970, 2850 (aliphatic C–H), 1520 (C···C of aromatic ring), 1680 (C=O) 1210 (C–N), 1120 (N–H)
2l′	386	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.25–7.60 (m, 12H, Ar–H), 5.50 (ss, 1H, indolic proton exchangeable with D_2O), 4.0 (d, 2H, –CH_2), 4.8 (t, 1H, NH)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N), 3150 (C–S)
2m′	266	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.30–7.90 (m, 7H, Ar–H), 5.0 (s, 1H, NHO*H*)	3420 (N–H), 3060 (aromatic C–H), 2970, 2870 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1220 (C–N), 3300 (O–H)
2n′	413	5.70 (s, 1H, –CO–N*H*), 5.50 (hump, 1H, –N*H*–CH_2), 5.25–4.00 (m, 4H, CH_2–CH_2), 8.20–7.55 (m, 10H, Ar–H), 11.60 (s, 1H, COO*H*)	3420 (N–H), 3020 (aromatic C–H), 2980, 2850 (aliphatic C–H), 1560 (C···C of aromatic ring), 1660 (C=O) 1230 (C–N), 3380 (O–H), 1720 (C=O of carboxylic group)
2o′	492	5.70 (s, 1H, –CO–N*H*), 5.50 (hump, 1H, –N*H*–CH_2), 5.25–4.00 (m, 4H, CH_2–CH_2), 8.40–7.95 (m, 9H, Ar–H), 11.80 (s, 1H, COO*H*)	3420 (N–H), 3020 (aromatic C–H), 2980, 2850 (aliphatic C–H), 1560 (C···C of aromatic ring), 1660 (C=O) 1230 (C–N), 3380 (O–H), 1720 (C=O of carboxylic group)
2p′	305	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.00 (m, 4H, CH_2–CH_2), 8.30–7.55 (m, 12H, Ar–H)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N)
2q′	395	5.85 (s, 1H, –CO–N*H*), 5.60 (hump, 1H, –N*H*–CH_2), 5.30–4.15 (m, 4H, CH_2–CH_2), 8.35–7.70 (m, 10H, Ar–H), 5.70 (hump 1H, N*H*–Ar exchangeable with D_2O)	3410 (N–H), 3040 (aromatic C–H), 2960, 2880 (aliphatic C–H), 1550 (C···C of aromatic ring), 1670 (C=O) 1210 (C–N), 1380 (NO_2)
2r′	334	5.70 (s, 1H, –CO–N*H*), 5.50 (hump, 1H, –N*H*–CH_2), 5.25–4.00 (m, 4H, CH_2–CH_2), 8.40–7.80 (m, 11H, Ar–H), 11.80 (s, 1H, COO*H*)	3420 (N–H), 3020 (aromatic C–H), 2980, 2850 (aliphatic C–H), 1560 (C···C of aromatic ring), 1660 (C=O) 1230 (C–N), 3370 (O–H), 1720 (C=O of carboxylic group)

(continued)

Table IV. (Continued)

Compound	$[M]^+$ m/z	^{1}H-NMR ($CDCl_3$) δ (ppm)	IR (KBr) (cm^{-1})
2s′	569	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.10 (m, 4H, CH_2–CH_2), 7.70–6.40 (m, 10H, Ar–H), 9.55 (ss, 2H, 2 × N*H*CO), 4.00 (t, 2H, 2 × –CH), 3.20 (dd, 4H, 2 × –CH_2)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C⋯C of aromatic ring), 1210 (C–N), 1270 (N–N), 3330 (N–H), 1730, 1715, 1680 (C=O), 1660–1640 (–N=C)
2t′	549	5.80 (s, 1H, –CO–N*H*), 5.70 (hump, 1H, –N*H*–CH_2), 5.30–4.10 (m, 4H, CH_2–CH_2), 7.70–6.95 (m, 6H, Ar–H), 9.55 (ss, 2H, 2 × N*H*CO), 4.00 (t, 2H, 2 × –CH), 3.20 (dd, 4H, 2 × –CH_2)	3410 (N–H), 3050 (aromatic C–H), 2950, 2870 (aliphatic C–H), 1520 (C⋯C of aromatic ring), 1210 (C–N), 1270 (N–N), 3330 (N–H), 1730, 1715, 1680 (C=O), 1660–1640 (–N=C)

(containing active methylene group) in ethanol (50–70 mL), formaldehyde (0.02 mol) and amine (0.02 mol) (primary or secondary) were added dropwise and the reaction mixtures were refluxed for 1 h, distilled and poured onto ice. The separated solids were filtered, washed with petroleum ether and recrystallised from appropriate solvents. Physical, analytical and spectroscopic data are given in *tables II and IV*, respectively.

4.2. Pharmacology

4.2.1. Anti-inflammatory activity

Rats of either sex weighing 60–100 g were divided into groups of ten animals each. A solution of carrageenin (1.0 % in 0.9 % saline) 0.05 mL was injected under the planter aponeurosis of the right paw of the rat by the method of Winter et al. [12].

$$\text{Anti-inflammatory activity } (\%) = \frac{V_t - V_c}{V_t} 100$$

where V_t and V_c are the volumes of oedema in the drug-treated and the control groups. Phenylbutazone and indomethacin were used as the reference drugs for comparison.

4.2.2. Ulcerogenic liability

The ulcerogenic liability was determined in albino rats of either sex (60–100 g) following the method of Djahanguiri [13] as modified by Saxena et al. [14]. Albino rats of either sex were divided into groups of ten animals each (*table III*). Pregnancy was excluded in the female rats. The rats were made to fast for 24 h prior to the administration of drugs. Water was allowed ad libitum to the animals. Three different doses of some (acidic and non-acidic) compounds (orally as well as intraperitoneally) indomethacin and phenylbutazone (control) were given. The animals were sacrificed 8 h after drug treatment. The stomach, duodenum and jejunum were removed and examined with a hand lens for any evidence of (a) shedding of epithelium; (b) petechial and frank haemorrhages and (c) erosion or discrete ulceration with or without the presence of haemorrhage. The detection of any one of these conditions was considered to be an evidence for ulcerogenic activity.

4.2.3. Acute toxicity

The potent compounds were investigated for their acute toxicity (ALD_{50}) in Albino mice by following the method of Smith [15].

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