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AMIDE DERIVATIVES OF SULFONAMIDES AND ISONIAZID: SYNTHESIS AND BIOLOGICAL EVALUATION†

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Abstract: In the present study, various amide derivatives of sulfanilamide, sulfamethoxazole, sulfadiazine, dapsone and isoniazid have been synthesized by condensing them with appropriate 4-oxo-4-(4-substituted phenyl)butanoic acid moiety. The compounds have been evaluated for their antiinflammatory, ulcerogenic and antibacterial activities. Their structures were established on the basis of elemental analysis, ^{1}H NMR and mass spectral data. Some of the compounds were found to have significant antiinflammatory and antibacterial activities. Additionally, these derivatives were low in their ulcerogenic action, which is the main side effect of commonly used NSAIDs.

Keywords: amides, sulfonamide, isoniazid, antiinflammatory, ulcerogenic, antibacterial

Over the past few decades the bacterial resistance to antibiotics has become one of the most important problems of infections treatment. Searching for new compounds, which would combine a non specific activity against a broad spectrum of bacteria and low toxicity, seems to be a promising way to overcome that problem. The sulfonamides are ones of the least expensive drugs and this factor largely accounts for their greater extent of use in developing countries like India. They are used in urinary tract infections, meningitis, streptococcal pharyngitis, bacillary dysentery, trachoma, chancroid, malaria, toxoplasmosis, nocardiasis and conjunctivitis (1-3). Dapsone still remains the drug of choice for all forms of leprosy. They are generally taken orally in higher doses which cause nausea, vomiting and epigastric pain (3, 4).

Non-steroidal antiinflammatory drugs (NSAIDs) form a class of clinical agents that are most widely used world over because of their antiinflammatory, analgesic and antipyretic effects. The gastrointestinal toxicity of NSAIDs is one of the most challenging problems in medicinal chemistry (5, 6). Aroylpropanoic acids, a class of NSAIDs, are effective antiinflammatory agents and some of them are available in the market; however, they have been reported (7, 8) to have gastrointestinal side effects, as do other commonly used NSAIDs. Some studies suggest that the direct tissue contact of these agents plays an important role in the production of side effects (9, 10) and the reported literature confirms that gastrointestinal side effects of aroylpropanoic acids are due to the presence of free carboxylic group in the parent drug (7, 9). Earlier work from our laboratories (13) has shown that transformation of the carboxylate function of aroylpropionic acids into oxadiazole ring resulted in an improved antiinflammatory activity with reduced ulcerogenic effect.

In view of these points and in continuation of our work on aroylpropanoic acid derivatives and amides (11-13), It was considered worthwhile to study various amide derivatives of 4-oxo-4-(substituted phenyl)butanoic acids with sulfonamides and isoniazid in order to improve their efficacy and to decrease side effects. Therefore, four different 4-oxo-4-(substituted phenyl)butanoic acids were condensed with appropriate sulfonamide or isoniazid and their structures were established on the basis of elemental analysis, ^{1}H NMR and mass spectral data. These compounds were evaluated for their antiinflammatory, ulcerogenic and antibacterial activities.

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EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded on DPX-300 NMR spectrometer and BRUKER-400 Ultra Shield™ spectrometer. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values were found within ±0.4% of the theoretical values. The progress of the reactions was monitored on silica gel G plates using iodine vapors as visualizing agent. All solvents were distilled prior use.

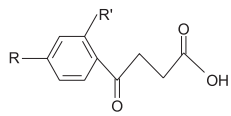
General method for the synthesis of 4-oxo-4-(substituted phenyl)butanoic acid (**1a-d**) (13)

Succinic anhydride (0.1 mole) was reacted with bromobenzene / toluene / diphenyl ether (50 mL) or biphenyl (0.1 mole in 50 mL of nitrobenzene) in the presence of anhydrous aluminium chloride (0.1125 mole). The reaction mixture was refluxed for 2-4 h and after completion of the reaction an excess solvent was removed by steam distillation. The residue was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give the desired 4-oxo-4-(substituted phenyl)butanoic acids (**1a-d**), which gave effervescence with sodium bicarbonate solution (Table 1).

General procedure for the synthesis of amides (**2a-l**, **3a-d**)

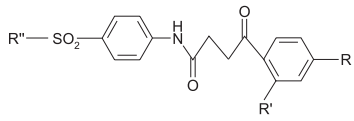
Amides were synthesized by dissolving 4-oxo-4-(substituted phenyl)butanoic acid (**1a-d**) (0.001 mol) and sulfanilamide / sulfadiazine / sulfamethoxazole / isoniazid (0.001 mol) or dapsone (0.0005 mol) in a minimum quantity of dry pyridine, separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 mL) dropwise, while maintaining the temperature below 5°C. The mixtures were stirred for another 0.5 h and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol to give **2a-l**, **3a-d** (Tables 2 and 3).

Table 1. Physical and spectral data of the 4-oxo-4-(substituted phenyl)butanoic acids (**1a-d**)



Compd.	R	R'	Mol. formula	Mol. weight	Yield %	M.p. °C	^{1}H NMR (δ ppm)
1a	Br–	H	$C_{10}H_9BrO_3$	257.1	62	108	2.53, 3.48 (t, each, 4H, 2 × -CH_2-), 7.52, 7.87 (d, each, A_2B_2, 4H, phenyl ring).
1b	CH_3–	CH_3–	$C_{12}H_{14}O_3$	208.22	50	92	2.78, 3.27 (t, each, 4H, 2 × -CH_2-), 3.35, 2.49 (s, each, 6H, 2 × -CH_3), 7.07 (m, 2H, H-3,5, phenyl ring), 7.65 (d, 1H, H-6).
1c	C_6H_5–	H	$C_{16}H_{14}O_3$	254.28	70	180	2.82, 3.37 (t, each, 4H, 2 × -CH_2-), 7.45 (m, 3H, H-3,4,5, phenyl ring), 7.64 (m, 2H, H-2,6, phenyl ring), 7.7, 8.07 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring).
1d	C_6H_5O–	H	$C_{16}H_{14}O_4$	270.28	65	172	2.80, 3.30 (t, each, 4H, 2 × -CH_2-), 7.17 (m, 3H, H-3,4,5, phenyl ring), 7.41 (m, 2H, H-2,6, phenyl ring), 7.7, 7.97 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring).

Table 2. Physical and spectral data of the amide derivatives of sulfonamides **(2a-l)**



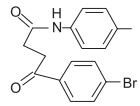
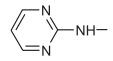
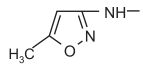
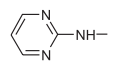
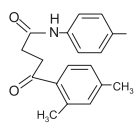
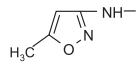
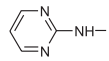
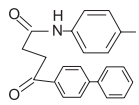
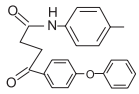
Compd.	R	R'	R''	Mol. formula; mass spectral data (m/z)	M. p. (^{o}C)	Yield %	^{1}H NMR (δ ppm)
2a	-Br	–H	H_2N–	$C_{16}H_{15}BrN_2O_4S$ 411 (M^+), 347, 331, 238, 184, 77 1	1 77-179	60	2.85, 3.37 (t, each, 4H, 2 × -CH_2-), 6.91 (s, 2H, -SO_2NH_2), 7.47, 7.81 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.8, 7.93 (d, each, A_2B_2, 4H, *p*-bromophenyl ring), 10.15 (s, 1H, -CONH-).
2b	-Br	–H		$C_{32}H_{26}Br_2N_2O_6S$ 726 (M^+ not observed), 238,184, 77	178-181	58	2.8, 3.56 (t, each, 4H, 2 × -CH_2-CH_2-), 7.68, 7.95 (d, each, 2 × A_2B_2, 8H, 2 × *p*-bromobenzene ring), 7.76, 8.11 (d, each, 2 × A_2B_2, 8H, 2 × *p*-substituted phenyl ring), 9.86 (s, 2H, 2 × -CONH-).
2c	-Br	–H		$C_{20}H_{17}BrN_4O_4S$ 489 (M^+), 471, 425, 240, 184, 156	142-144	54	2.85, 3.33 (t, each, 4H, 2 × -CH_2-), 6.91 (t, 1H, H-4, diazine ring), 7.28 (m, 2H, H-3,5, diazine ring), 7.71, 8.17 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.88, 7.98 (d, each, A_2B_2, 4H, *p*-bromobenzene ring), 10.12 (s, 1H, -CONH-).
2d	-Br	–H		$C_{20}H_{18}BrN_3O_5S$ 492 (M^+), 410, 238, 240, 77	168	62	2.36 (s, 3H, -CH_3), 2.83, 3.39 (t, each, 4H, 2 × -CH_2), 6.21 (s, 1H, isoxazole ring), 7.34, 7.59 (d, each, A_2B_2, 4H, *p*-bromobenzene ring), 7.67, 7.96 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 10.09 (s, 1H, -CONH-).
2e	-CH_3	–CH_3	H_2N–	$C_{18}H_{20}N_2O_4S$ 360 (M^+), 278, 187 133, 105	168-170	60	2.35, 2.47 (s, each, 6H, 2 × -CH_3), 2.79, 3.52 (t, each, 4H, 2 × -CH_2-), 6.81 (s, 2H, -SO_2NH_2), 7.07 (m, 2H, H-3,5, phenyl), 7.65 (d, 1H, H-6, phenyl), 7.72, 8.13 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 10.05 (s, 1H, -CONH-).
2f	-CH_3	–CH_3		$C_{22}H_{22}N_4O_4S$ 438 (M^+), 420, 187, 189, 133	156-158	58	2.34, 2.42 (s, each, 6H, 2 × -CH_3), 2.85, 3.34 (t, each, 4H, 2 × CH_2-), 6.93 (t, 1H, H-4, diazine ring), 7.08 (m, 2H, H-3,5, phenyl), 7.28 (m, 2H, H-3,5, diazine ring), 7.65 (d, 1H, H-6, phenyl), 7.71, 8.03 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 10.13 (s, 1H, -CONH-).
2g	-CH_3	–CH_3		$C_{36}H_{36}N_2O_6S$ 624 (M^+ not observed), 187, 189, 105	166-167	55	2.33, 2.53 (s, each, 12H, 4 × -CH_3), 2.89, 3.36 (t, each, 8H, 2 × -CH_2-CH_2-), 7.07 (m, 4H, 2 × H-3,5, phenyl), 7.65 (d, 2H, 2 × H-6), 7.75, 8.15 (d, each, 2 × A_2B_2, 8H, 2 × *p*-substituted phenyl ring), 10.09 (s, 2H, 2 × -CONH-).

Table 2. cont.

Compd.	R	R'	R''	Mol. formula; mass spectral data (m/z)	M. p. (°C)	Yield %	^{1}H NMR (δ ppm)
2h	-CH_3	–CH_3		$C_{22}H_{23}N_3O_5S$ 441 (M^+), 359, 377, 189, 133, 105	175-177	63	2.34, 2.49 (s, each, 6H, 2 × -CH_3), 2.37 (s, 3H, -CH_3, isoxazole), 2.87, 3.35 (t, each, 4H, 2 × -CH_2-), 6.15 (s, 1H, isoxazole ring), 7.06 (m, 2H, H-3,5, phenyl), 7.66 (d, 1H, H-6, phenyl), 7.27, 7.87 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 10.11 (s, 1H, -CONH-).
2i	C_6H_5-	H		$C_{26}H_{22}N_4O_4S$ 486 (M^+), 468, 404, 235, 181, 153	184	58	2.86, 3.42 (t, each, 4H, 2 × -CH_2-), 6.93 (t, 1H, H-4, diazine ring), 7.28 (m, 2H, H-3,5, diazine ring), 7.4-7.62 (m, 5H, phenyl), 7.71, 7.78 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.84, 8.06 (d, each, A_2B_2, 4H, sulfanilamide ring), 9.98 (s, 1H, -CONH-).
2j	C_6H_5-	H		$C_{44}H_{36}N_2O_6S$ Not taken	213-215	70	2.89, 3.34 (t, each, 8H, 2 × -CH_2-CH_2-), 6.8-8.4 (complex m, 22H, Ar), 10.06 (s, 2H, 2 × -CONH-).
2k	C_6H_5O-	H	H_2N–	$C_{22}H_{20}N_2O_5S$ 424 (M^+), 342, 253, 197, 169	194-195	58	2.81, 3.47 (t, each, 4H, 2 × -CH_2-), 6.87 (s, 2H, -SO_2NH_2), 6.97, 7.6 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.94, 7.97 (d, each, A_2B_2, 4H, sulfanilamide ring), 6.8-7.2 (m, 5H, phenyl), 10.23 (s, 1H, -CONH-).
2l	C_6H_5O-	H		$C_{44}H_{36}N_2O_8S$ 652 (M^+ not observed), 570, 253, 169, 77	226	72	2.83, 3.36 (t, each, 8H, 2 × -CH_2-CH_2-), 6.7-8.3 (complex m, 22H, Ar), 10.11 (s, 2H, 2 × -CONH-).

Biological evaluation

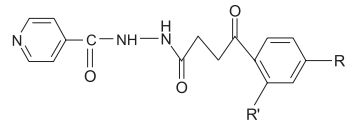
Antiinflammatory and acute ulcerogenic activities were performed on albino rats of Wistar strain of either sex, weighing 180-200 g. Pregnant females were excluded. The animals were housed and treated in accordance with the guidelines of Institutional Animal Ethics Committee (IAEC). The animals were housed in groups of six (Animal house, Hamdard University, New Delhi, India) and acclimatized to room conditions for at least 2 days before the experiments. The feeding was stopped the day before the experiment, but the animals were allowed free access to water.

Antiinflammatory activity

The synthesized compounds were evaluated for their antiinflammatory activity using carrageenan-induced rat paw edema method of Winter et al. (14). The animals were randomly divided into groups of six animals each. Group I was kept as a control and received only 0.5% carboxymethyl cellulose (CMC) solution. Group II was kept as a standard and received indomethacin (10 mg/kg *p.o.*). Carrageenan solution (0.1% in sterile 0.9% NaCl solution) in a volume of 0.1 mL was injected subcutaneously into the sub-plantar region of the right hind paw of each rat, 30 min after the administration of the test compounds and standard drugs. The paw volume was measured by saline displacement shown on screen of digital plethysmometer (Panlab) at 2 and 3 h after carrageenan injection. Thus the edema volume in control group (Vc) and edema volume in groups treated with test compounds (Vt) was measured and the percentage inhibition of edema was calculated using the formula:

Antiinflammatory activity (% inhibition) = [(Vc-Vt)/Vc] × 100

Table 3. Physical and spectral data of the amide derivatives of isoniazid **(3a-d)**



Compd	R	R'	Mol. formula; mass spectral data (m/z)	M.p. (°C)	Yield %	^{1}H NMR (δ ppm)
3a	Br-	H-	$C_{16}H_{14}BrN_3O_3$ 376 (M^+), 358, 240, 184, 156, 105	131-133	55	2.81, 3.36 (t, each, 8H, 2 × -CH_2-CH_2-), 7.46, 7.91 (d, each, A_2B_2, 4H, *p*-bromophenyl ring), 8.03, 8.75 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.26, 9.66 (s, each, 2H, 2 × -NH-).
3b	CH_3-	CH_3-	$C_{18}H_{19}N_3O_3$ 325 (M^+), 189, 133, 105	128-130	57	2.37, 2.48 (s, each, 6H, 2 × -CH_3), 2.77, 3.28 (t, each, 4H, 2 × -CH_2-), 7.09 (m, 2H, H-3,5, phenyl ring), 7.67 (d, 1H, H-6, phenyl ring), 7.85, 8.81 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.08, 9.23 (s, each, 2H, 2 × -NH-).
3c	C_6H_5-	H-	$C_{22}H_{19}N_3O_3$ 373 (M^+), 237, 181, 153	184-186	62	2.82, 3.35 (t, each, 4H, 2 × -CH_2), 7.42 (m, 3H, H-3,4,5, phenyl ring), 7.64 (m, 2H, H-2,6, phenyl ring), 7.68, 8.03 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 8.11, 8.83 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.19, 9.63 (s, each, 2H, 2 × -NH-).
3d	C_6H_5O-	H-	$C_{22}H_{19}N_3O_4$ 389 (M^+), 371, 251, 197	135-137	68	2.79, 3.28 (t, each, 4H, 2 × -CH_2-), 6.97, 7.95 d, each, A_2B_2, (4H, *p*-substituted phenyl ring), 7.17 (m, 2H, H-2,6, phenyl ring), 7.23 (m, 1H, phenyl ring), 7.44 (m, 2H, H-3,5, phenyl ring), 7.91, 8.81 d, each, A_2B_2, (4H, *p*-substituted phenyl ring), 9.23, 9.65 (s, each, 2H, 2 × -NH-).

Ulcerogenic activity

Acute ulcerogenic activity determination was performed according to the method of Cioli et al. (9). The rats were divided into twelve groups consisting of six animals in each group. Group I was kept as a control and received only vehicle (suspension of 1% methylcellulose). The activity was evaluated after oral administration of test compounds or indomethacin at a dose of 60 mg/kg. The food was withdrawn on the day before the experiment, but free access to water was allowed. The animals were fed normal diet for 17 h after the drug treatment and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The gastric mucosa was examined for damage by means of a magnifying glass. The severity of mucosal damage for each stomach was assessed according to the following scoring system:
0.5 – redness; 1.0 – spot ulcers; 1.5 – hemorrhagic streaks; 2.0 – ulcers > 3 but ≤ 5; 3.0 – ulcers > 5.

The mean score of each treated group minus the mean score of the control group was considered as the severity index of gastric mucosal damage.

Antibacterial study

All the newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC-29737), *Escherichia coli* (ATCC-8739) and *Pseudomonas aeruginosa* (NCLM-2035) at a concentration of 100 mg/mL by turbidity method (15). Compounds inhibiting growth of one or more of the above microorganisms were further tested for minimum inhibitory concentration (MIC). Solvent (DMF) and growth controls were kept. MICs values were determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of the test compound and controls were inoculated with approximately 5×10^5 c.f.u. of actively dividing bacteria cells. The cultures were incubated for 24 h at 37°C and the growth was monitored visually and spectrophotometrically. Ciprofloxacin was used as a standard drug for comparison. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as MIC.

RESULTS AND DISCUSSION

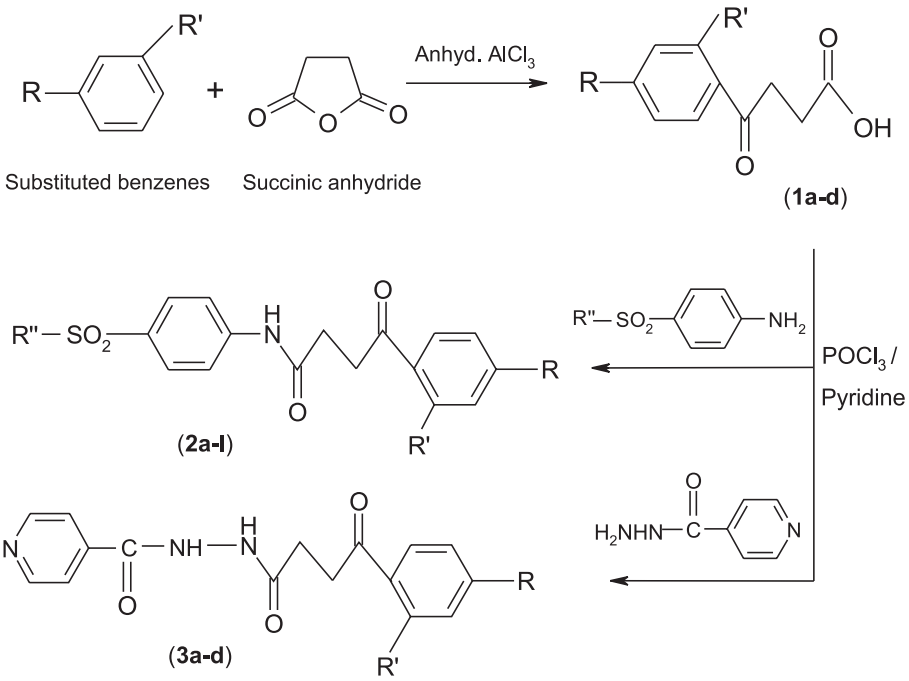
Chemistry

The synthesis of the title compounds was per-

Table 4. Antiinflammatory and ulcerogenic activities of the title compounds

Compound	Antiinflammatory activity (% inhibition ± S.E.M.)†		Ulcerogenic activity (severity index ± S.E.M.)
	After 2 h	After 3 h	
Control	-	-	0.00
Indomethacin	52.01 ± 4.27	66.24 ± 2.1	2.25 ± 0.21
2a	14.44 ± 2.45**	38.01 ± 2.05**	0.83 ± 0.25**
2b	21.23 ± 1.96**	48.41 ± 3.54**	1.16 ± 0.25**
2d	25.91 ± 1.91**	57.11 ± 3.54	1.50 ± 0.28
2f	37.36 ± 3.35**	54.35 ± 3.72*	1.00 ± 0.18**
2h	54.77 ± 2.56	61.78 ± 1.43	1.25 ± 0.21*
2i	4.25 ± 1.01**	18.25 ± 1.93**	0.75 ± 0.11**
2j	11.25 ± 2.84**	30.57 ± 2.39**	0.83 ± 0.21**
2l	15.72 ± 1.16**	41.41 ± 1.95**	0.91 ± 0.35**
3a	6.16 ± 1.46**	8.49 ± 1.33**	0.5 ± 0.13**
3d	7.64 ± 1.43**	28.66 ± 2.37**	0.41 ± 0.15**

†Relative to the standard (Indomethacin) and data were analyzed by one-way ANOVA followed by Dunnett's multiple comparison test for n = 6 ; **p < 0.01; *p < 0.05



Scheme 1. Protocol for synthesis of amide derivatives (**2a-1, 3a-d**)

formed in a one-pot reaction method and is presented in Scheme 1. In the initial step, 4-oxo-4-(substituted phenyl)butanoic acids (**1a-d**) were prepared by condensing substituted benzenes with succinic anhydride in the presence of anhydrous aluminium chloride following Friedel-Crafts acylation reaction conditions (13). The desired amides (**2a-l**, **3a-d**) were synthesized by reacting 4-oxo-4-(substituted phenyl)butanoic acids (**1a-d**) with sulfonamide moiety (sulfanilamide/sulfadiazine/sulfamethoxazole) or isoniazid in dry pyridine in the presence of phosphorous oxychloride as condensing agent and obtained in appreciable yields (54-72%). The purity of the compounds was controlled by TLC in solvent

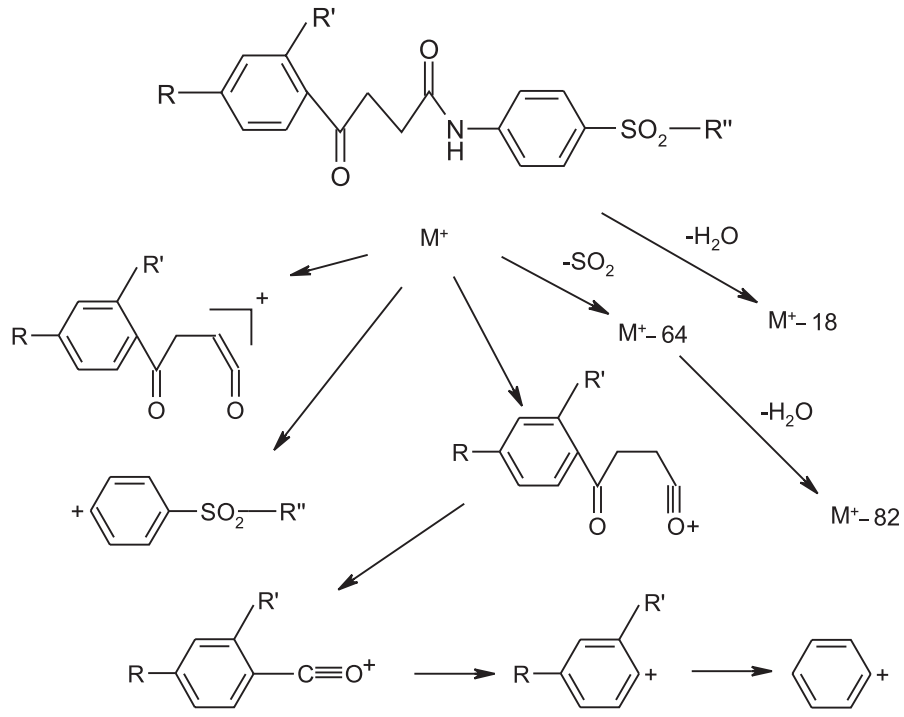


Chart. 1. Mass fragmentation pattern of amide derivatives (**2a-l**)

system toluene:ethyl acetate:formic acid (5:4:1, v/v/v). Spectral data and microanalysis data were in agreement with the proposed structures. The physical and analytical data are recorded in Tables 1-3.

Nuclear magnetic resonance spectra (^{1}H NMR; δ ppm) showed two triplets at around 2.55 and 3.53 ppm (-CH_2-CH_2-) and signals in the region 6.5-7.9 ppm (aryl protons). The mass spectra showed molecular ion peaks of reasonable intensities, supporting the structure. However, in case of compounds derived from dapsone, molecular ion peak could not be observed. The following points could be made regarding the mass fragmentation pattern of compounds **2a-l**: There was splitting of Ar-$COCH_2CH_2$-CON- bond resulting in formation of Ar-$COCH_2CH_2$-C≡O^+ ion (fragment-1) or [Ar-$COCH_2CH$=C=O]$^+$ ion (fragment-2) and/or [R''-SO_2-Ph]$^+$. These fragments could be important for diagnosis of successful formation of the product, corresponding to their parent 4-oxo-4-(substituted phenyl)butanoic acid moiety and sulfonamide moiety, respectively. Fragment-1/2 further splitted to Ar-C≡O^+ and to Ar^+ and then to $C_6H_5^+$ (m/z=77). There was a loss of 18 / 64 / 82 mass units, may be due to loss of H_2O / SO_2 / SO_2 + H_2O molecule(s), respectively. The fragmentation pattern is presented in Chart 1. In case of compounds **3a-d**, there was a splitting of Ar-$COCH_2CH_2$-CON- bond resulting in formation of [Ar-$COCH_2CH_2$-C≡O] ion$^+$ (fragment-1) or [Ar-$COCH_2CH$=C=O]$^+$ ion (fragment-2) and/or [C_5H_4N-C≡O]$^+$. These fragments provided important evidence for successful formation of the product. The fragment, [C_5H_4N-C≡O]$^+$, further splitted to $C_5H_4N^+$. The fragmentation pattern is presented in Chart 2.

Antiinflammatory activity

The *in-vivo* antiinflammatory activities of the synthesized compounds (**2a**, **2b**, **2d**, **2f**, **2h**, **2i**, **2j**, **2l**, **3a and 3d**) were evaluated at 10 mg/kg oral dose and were compared with that of the standard drug indomethacin at the same oral dose. The obtained pharmacological results revealed that the amides derived from sulfamethoxazole were highly active compounds; **2d** and **2h** showed 57.11% and 61.78% inhibition, respectively, and their activity was comparable to that of the standard drug indomethacin (66.24%) at the same dose level. Another compound, **2f,** showed good activity with 54.35% inhibition. The amides derived from isoniazid (**3a** & **3d**) were low in their antiinflammatory action. The results indicate that compounds having

Table 5. Antibacterial activity of the title compounds (**2a-l**, **3a-d**)

Compound	Minimum inhibitory concentration (MIC)		
	S. aureus	*E. coli*	*P. aeruginosa*
Control	-	-	-
Ciprofloxacin	6.25	6.25	6.25
2a	12.5	12.5	50
2b	> 100	> 100	> 100
2c	25	50	50
2d	> 100	> 100	> 100
2e	25	25	50
2f	50	25	50
2g	> 100	> 100	> 100
2h	> 100	> 100	> 100
2i	> 100	> 100	> 100
2j	> 100	> 100	> 100
2k	25	25	12.5
2l	> 100	> 100	> 100
3a	50	25	50
3b	> 100	50	50
3c	> 100	> 100	> 100
3d	> 100	> 100	> 100

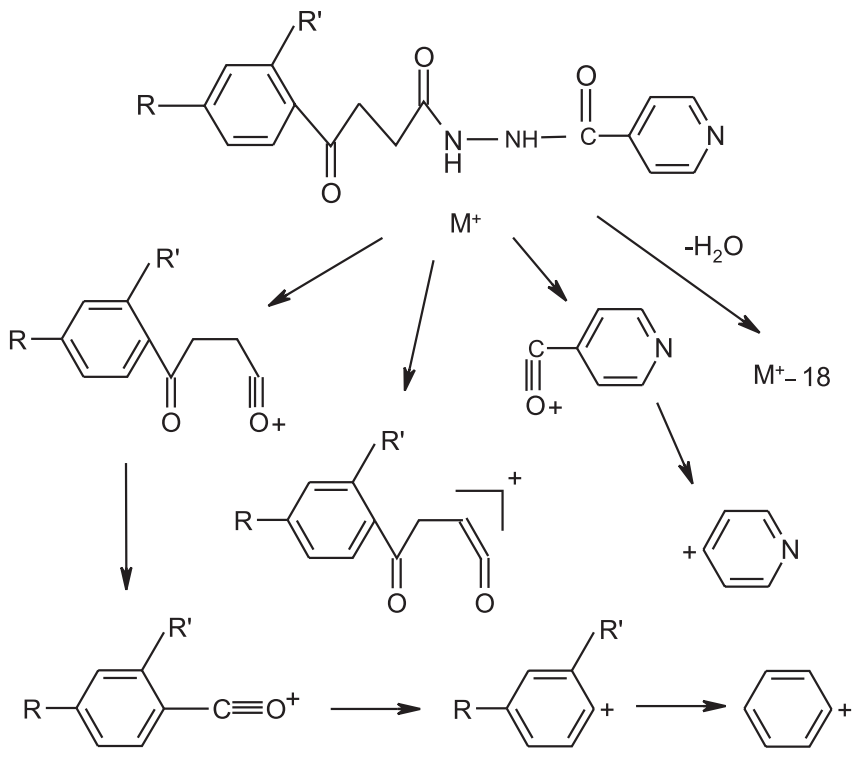


Chart. 2. Mass fragmentation pattern of amide derivatives (**3a-d**)

bromo/methylbenzoyl propanoic acid and/or sulfamethoxazole moiety as promoiety have high degree of activity (Table 4).

Ulcerogenic activity

The title compounds were screened for their ulcerogenic activity in albino rats after oral administration of test compounds or indomethacin at the dose of 60 mg/kg. The tested compounds showed low ulcerogenic activity ranging from 0.41 to 1.5, whereas the standard drug indomethacin showed high severity index, 2.25 (Table 4). The maximum reduction in ulcerogenic activity was found in the amides derived from isoniazid (**3a**, **3d**). All the tested compounds exhibited better gastro-intestinal profile as compared to the standard drug indomethacin.

Antibacterial activity

The antibacterial activity of the compounds was evaluated against *S. aureus*, *E. coli* and *P. aeruginosa* at a concentration of 100 mg/mL. Broth dilution technique was followed for determining minimum inhibitory concentration (MIC) of the compounds. Ciprofloxacin was used as a standard drug for comparison, which showed MIC = 6.25 mg/mL against all the three bacterial strains. Compound **2a** showed very good activity against *S. aureus* and *E. coli* with MIC of 12.5 μg/mL. A similar type of activity was shown by compound **2k** against *P. aeruginosa* at 12.5 μg/mL concentration. Compounds **2e**, **2f**, **2k** and **3a** showed significant activity against *E. coli* with MIC of 25.0 μg/mL. Compounds **2c**, **2e** and **2k** were also good in their action against *S. aureus* with MIC of 25.0 μg/mL. Other compounds were moderate in their action. From the antibacterial results, it was observed that the compounds having free amino function (**2a**, **2e,** **2k**) were the most active among the tested (Table 5).

CONCLUSIONS

We obtained herein two new compounds (**2d** and **2h**) with antiinflammatory activity comparable to that of indomethacin (standard drug), at the same dose level (10 mg/kg). Additionally, these derivatives were very low in their ulcerogenic action, which is the main side effect of commonly used NSAIDs. Compound **2a** showed very good activity against *S. aureus* and *E. coli* with MIC of 12.5 μg/mL. These results confirmed the importance of exploration of old drugs as a safer template to built new prodrug candidates. It can be concluded that this class of amides holds promise towards the pursuit to develop agents with improved pharmacological profile.

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