NEW AMIDES OF SULPHONAMIDES: SYNTHESIS AND BIOLOGICAL EVALUATION

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(Received: April 13, 2009 - Accepted: December 17, 2009)

SUMMARY

A series of amide-derivatives has been synthesized by establishing an amide linkage (-CONH-) between appropriate sulphonamide moiety and different 3-(4-substituted-benzoyl) propionic acids through one-pot reaction. The structures of the newly synthesized compounds were established on the basis of modern analytical techniques. These amides were evaluated for their antiinflammatory, ulcerogenic and antibacterial activities. Some of the compounds showed good antiinflammatory activity. Additionally, these derivatives were very low in their ulcerogenic action.

Keywords: Amide, antiinflammatory, sulphonamide, antibacterial.

INTRODUCTION

The gastrointestinal toxicity of acidic non-steroidal antiinflammatory drugs (NSAIDs) is one of the most challenging problems in medicinal chemistry[1]. NSAIDs form a class of therapeutic agents that are most widely used world over because of their antiinflammatory, analgesic and antipyretic effects. 3-(4-Substituted benzoyl)propionic acids belong to well known aroylpropionic acid class of non steroidal antiinflammatory agents. Aroylpropionic acids are effective antiinflammatory agents and some of them are available in the market, however, they are associated with gastrointestinal side effects; a common feature of NSAIDs[2-4]. Studies suggest that the direct tissue contact of these agents plays an important role in the production of side effects and the reported literature confirms that gastrointestinal side effects of aroylpropionic acids are due to presence of free carboxylic group in the parent drug[3,4].

Sulphonamides are one 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 pharyngytis, bacillary dysentery, trachoma, cancroids, malaria, toxoplasmosis, nocardiasis and conjunctivitis[5-7]. 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[7].

There are conditions when an inflammation occurs in response to a microbial infection, and a combination of the antiinflammatory drug with antimicrobial agent is prescribed in such conditions. These combinations often cause side effects because of high doses of drugs. Searching for new compounds, which would combine two activities seem to be promising way to overcome that problem[8]. In view of these points and in continuation of our work on novel amides[9,10], It was considered worthwhile to study various amide-derivatives of sulphonamides with 3-aroylpropionic acids in order to improve their efficacy and to decrease side effects.

EXPERIMENTAL

Chemistry

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates, with the solvent system: toluene-ethyl acetate-formic acid (5:4:1, v/v/v). The spots were located under iodine vapours and UV light. Elemental analyses were performed on a Perkin-Elmer 240 analyzer and the values were in range of ±0.4% for each element analyzed (C, H, N). ^{1}H-NMR spectra were recorded on Varian E-360 MHz or Bruker spectropsin DPX-300MHz with tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. The progress of the reactions was monitored on silica gel G plates using iodine vapors as visualizing agent.

Preparation of 3-(4-substituted benzoyl)propionic acid (1-4)

Succinic anhydride (0.1 mole) was reacted with an appropriate aromatic compound (substituted benzene; 50 mL) in presence of anhydrous aluminium chloride (0.1125 moles). The reaction mixture was refluxed under anhydrous conditions for two hours and after completion of the reaction excess solvent was removed by steam distillation. On cooling, a solid mass separated out which was filtered and 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 recrystallized from methanol to give **1-4**.

3-(4-Chlorobenzoyl)propionic acid (**1**). Yield 72%; M.p. 124° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.81 & 3.38 (t, e, 2x -CH_2-), 7.45 & 7.92 (d, each, A_2B_2, *p*-substituted phenyl).

3-(4-Methoxybenzoyl)propionic acid (**2**). Yield 88%; M.p. 152° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.80 & 3.28 (t, e, 2x -CH_2-) 3.88 (s, 3H, -OCH_3), 6.94 & 7.97 (d, each, A_2B_2, *p*-substituted phenyl).

3-(4-Methylbenzoyl)propionic acid (**3**). Yield 66%; M.p. 106° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.65 & 3.26 (t, e, 2x -CH_2-) 2.37 (s, 3H, -CH_3), 7.27 & 7.85 (d, each, A_2B_2, *p*-substituted phenyl).

3-(4-Ethylbenzoyl)propionic acid (**4**). Yield 75%; M.p. 110° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.25 (t, 3H, $\underline{CH_3}CH_2$-), 2.69 (q, 2H, $CH_3\underline{CH_2}$-), 2.80 & 3.30 (t, each, 2x -CH_2-), 7.27 & 7.90 (d, each, A_2B_2, 4H, *p*-substituted phenyl).

General procedure for the synthesis of amides (5-14)

Amides were synthesized by dissolving 3-(4-substituted-benzoyl) propanoic acid (**1-4**) (0.001 mol) and sulfanilamide / sulfadiazine / sulfamethoxazole / isoniazid (0.001 mol) or dapsone (0.0005 mol) in minimum quantity of dry pyridine separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9ml) drop wise while maintaining the temperature below 5 °C. The contents were stirred for another half-hour 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 **5-14** (Table 2).

N[1]-[4-(2-Pyrimidinylsulfamoyl)phenyl]-4-(4-chlorophenyl)-4-oxobutanamide (**5**): Yield: 54 %; m.p. 166-168 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.84 & 3.36 (t, each, 2x -CH_2-), 6.94 (t, 1H, H-4, diazine ring), 7.25 (m, 2H, H-3,5, diazine ring), 7.73 & 8.31 (d, each, A_2B_2, *p*-substituted phenyl ring), 7.87 & 7.95 (d, each, A_2B_2, 4H, *p*-chlorobenzene ring), 10.03 (s, 1H, -CONH-); MS (*m/z*): 444 (M^+), 380, 234, 195, 139, 77; Anal. $C_{20}H_{17}Cl\,N_4O_4S$, calcd. C, 54.00; H, 3.85; N, 12.59; found C, 54.12; H, 3.76; N, 12.52.

N[1]-[4-(5-Methyl-3-isoxazolylsulfamoyl)phenyl]-4-(4-chlorophenyl)-4-oxobutanamide (**6**): Yield: 62 %; m.p 179-180 ° C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.32 (s, 3H, -CH_3), 2.81 & 3.53 (t, each, 2x -CH_2), 6.18 (s, 1H, methoxazole ring), 7.29 & 7.87 (d, each, A_2B_2, 4H, *p*-chlorobenzene ring), 7.44 & 7.91 (d each, A_2B_2, 4H, *p*-substituted phenyl ring), 9.98 (s, 1H, -CONH-); MS (*m/z*): 447 (M^+), 383, 237, 139, 77; Anal. $C_{20}H_{18}Cl\,N_3O_5S$, calcd. C, 53.63; H, 4.05; N, 9.38; found C, 53.45; H, 4.12; N, 9.34.

N[1]-(4-Sulfamoylphenyl)-4-(4-methoxyphenyl)-4-oxobutanamide (**7**): Yield: 60 %; m.p 168° C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.64 (s, 3H, -OCH_3), 2.87 & 3.51 (t, each, 2x -CH_2-), 6.86 (s, 2H, -SO_2NH_2), 7.56 & 7.83 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.73 & 7.97 (d, each, A_2B_2, 4H, *p*-anisole ring), 10.11 (s, 1H, -CONH-).; MS (*m/z*): 362 (M^+), 190, 135, 107; Anal. $C_{17}H_{18}N_2O_5S$, calcd. C, 56.34; H, 5.01; N, 7.73; found C, 56.42; H, 5.05;

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N, 7.58.

N[1]-[4-(2-Pyrimidinylsulfamoyl)phenyl]-4-(4-methoxyphenyl)-4-oxobutanamide (**8**): Yield: 58 %; m.p. 154 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.54 (s, 3H, -OCH_3), 2.83 & 3.34 (t, each, 2x -CH_2-), 6.92 (t, 1H, H-4, diazine ring), 7.26 (m, 2H, H-3, 5, diazine ring), 7.68 & 8.04 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.76 & 7.95 (d, each, A_2B_2, 4H, *p*-anisole ring), 9.53 (s, 1H, -CONH-).; MS (*m/z*): 440 (M^+), 358, 234, 190, 135, 77; Anal. $C_{21}H_{20}N_4O_5S$, calcd. C, 57.26; H, 4.58; N, 12.72; found C, 57.08; H, 4.61; N, 12.65.

N[1]-[4-(5-Methyl-3-isoxazolylsulfamoyl)phenyl]-4-(4-methoxylphenyl)-4-oxobutanamide (**9**): Yield: 63 %; m.p. 176-178 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.03 (s, 3H, -CH_3, methoxazole), 2.58 (s, 3H, -OCH_3), 2.83 & 3.37 (t, each, 2x -CH_2-), 6.15 (s, 1H, methoxazole ring), 7.27 & 7.87 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.48 & 7.75 (d, each, A_2B_2, 4H, *p*-anisole ring), 9.60 (s,1H,-CONH-); MS (*m/z*): 443 (M^+), 425, 379, 237, 131, 77; Anal. $C_{21}H_{21}N_3O_6S$, calcd. C, 56.88; H, 4.77; N, 9.48; found C, 56.67; H, 4.82; N, 9.51.

N[1]-[4-(5-Methyl-3-isoxazolylsulfamoyl)phenyl]-4-(4-methylphenyl)-4-oxobutanamide (**10**): Yield: 65 %; m.p. 186-188 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.33(s, 3H, -CH_3, methoxazole), 2.45(s, 3H, -CH_3), 2.82 & 3.37 (t each, 2x -CH_2-), 6.17 (s, 1H, methoxazole ring), 7.72 & 8.1 (d, each, A_2B_2, 4H, *p*-substituted phenyl ring), 7.76 & 7.81 (d, each, A_2B_2, 4H, *p*-toluene ring), 9.36 (s, 1H, -CONH-): MS (*m/z*): 427 (M^+), 409, 345, 175, 119, 91; Anal. $C_{21}H_{21}N_3O_5S$, calcd. C, 59.01; H, 4.95; N, 9.83; found C, 58.85; H, 5.03; N, 9.78.

N[1]-(4-{4-[3-(4-Methylphenyl)-3-oxopropylcarboxamido]phenylsulfonyl} phenyl)-4-(4-methyl phenyl)-4-oxobutanamide (**11**): Yield: 70 %; m.p. 206-208 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.41 (s, 6H, 2x -CH_3) 2.89 & 3.34 (t, each, 2x -CH_2-CH_2-), 7.52 & 7.87 (d, each, 2x A_2B_2, 8H, 2x *p*-toluene ring), 7.68 & 7.94 (d, each, 2x A_2B_2, 8H, 2x *p*-substituted phenyl ring), 9.59 (s, 2H, 2x -CONH-); MS: *m/z* 596 (M^+), 360, 175, 119, 91, 77; Anal. $C_{34}H_{32}N_2O_6S$, calcd. C, 68.44; H, 5.41; N, 4.69; found C, 68.51; H, 5.36; N, 4.64.

N[1]-(4-{4-[3-(4-Chlorophenyl)-3-oxopropylcarboxamido]phenylsulfonyl} phenyl)-4-(4-chloro phenyl)-4-oxobutanamide (**12**): Yield: 57 %; m.p. 196 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.84 & 3.36 (t, each, 2x -CH_2-CH_2-), 7.66 & 7.87 (d, each, 2x A_2B_2, 8H, 2x *p*-chlorobenzene ring), 7.71 & 8.16 (d, each, 2x A_2B_2, 8H, 2x *p*-substituted phenyl ring), 9.74 (s, 2H, 2x -CONH-); MS: *m/z* 637 (M^+), 473, 195, 139, 105, 77; Anal. $C_{32}H_{26}Cl_2N_2O_6S$, calcd. C, 60.29; H, 4.11; N, 4.39; found C, 60.43; H, 4.15; N, 4.26.

N[1]-(4-{4-[3-(2-Methoxyphenyl)-3-oxopropylcarboxamido] phenylsulfonyl}phenyl)-4-(4-methoxy phenyl)-4-oxobutanamide (**13**): Yield: 55 %; m.p. 166 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.56 (s, 3H, -OCH_3), 2.89 & 3.36 (t, each, 2x -CH_2-CH_2-), 7.68 & 7.95 (d, each, 2x A_2B_2, 8H, 2x *p*-anisole ring), 7.75 & 8.15 (d, each, 2x A_2B_2, 8H, 2x *p*-substituted phenyl ring), 9.60 (s, 2H, 2x -CONH-); MS (*m/z*): 628 (M^+ not observed), 135, 107, 77; Anal. $C_{34}H_{32}N_2O_8S$, calcd. C, 64.96; H, 5.13; N, 4.46; found C, 64.88; H, 5.19; N, 4.42.

N[1]-(4-{4-[3-(4Ethylphenyl)-3-oxopropylcarboxamido]phenylsulfonyl} phenyl)-4-(4-ethylphenyl)-4-oxobutanamide (**14**): Yield: 72 %; m.p. 166 °C; ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.27 (t, 6H, 2x $\underline{CH_3}CH_2$-), 2.58 (q, 4H, 2x $CH_3\underline{CH_2}$-), 2.82 & 3.38 (t, each, 2x -CH_2-CH_2-), 7.28 & 7.93 (d, each, 2x A_2B_2, 8H, 2x *p*-ethylbenzene ring), 7.76 & 8.13 (d, each, 2x A_2B_2, 8H, 2x *p*-substituted phenyl ring), 10.03 (s, 2H, 2x -CONH-); MS: *m/z* 624 (M^+), 189, 133, 105, 91, 77; Anal. $C_{36}H_{36}N_2O_6S$, calcd. C, 69.21; H, 5.81; N, 4.48; found C, 69.35; H, 5.87; N, 4.33.

Biological evaluation

Antiinflammatory and ulcerogenic activities were performed on Wistar rats of either sex, weighing 180-200 g. 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 they 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*[11]. The animals were randomly divided into groups of six. Group I was kept as control, and received only 0.5% carboxymethyl cellulose (CMC) solution. Groups II was kept as 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 minutes after the administration of the test compounds and standard drugs. The paw volume was measured by saline displacement shown on screen of digital Plethysmometer at 2 and 3 hrs 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]x100

Acute ulcerogenic activity

Acute ulcerogenic activity was performed according to the method of Cioli et al.[4]. The rats were divided into twelve groups consisting of six animals in each group. Group I was kept as control, and received only vehicle (suspension of 1% methyl cellulose). The activity was evaluated after oral administration of test compounds or indomethacin at the 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.

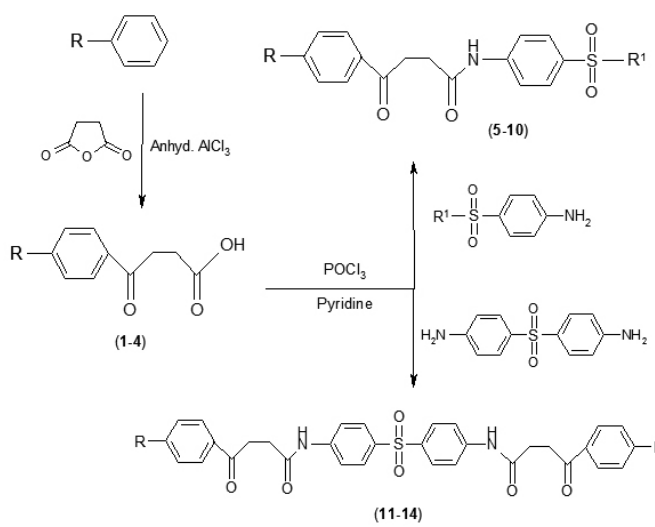
The mean score of each treated group minus the mean score of the control group was considered as severity index of gastric mucosal damage.

Antibacterial activity

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[12]. 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. Minimum inhibitory concentrations (*MICs*) were determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 5x10^5 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 standard drug for comparison. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as *MIC*.

RESULTS AND DISCUSSION

Chemistry



Scheme 1. Protocol for synthesis of titled amides (**5-14**).

Titled compounds (**5-14**) were synthesized through one-pot reaction method as depicted in Scheme 1. In the initial step, 3-aroylpropionic acids (**1-4**) were prepared by condensing substituted benzenes with succinic anhydride following Friedel-Craft's acylation reaction conditions. The desired amides (**5-14**) were synthesized by reacting 3-aroylpropionic acids (**1-4**) with appropriate

sulphonamide moiety in dry pyridine in presence of phosphorous oxychloride ($POCl_3$) as condensing agent and obtained in appreciable yields (54-72%). The purity of the compounds was controlled by TLC in solvent system toluene:ethyl acetate:formic acid (5:4:1, v/v/v). Spectral data and microanalysis data were in agreement with the proposed structures.

In the nuclear magnetic resonance spectra (^{1}H NMR; *d* ppm) showed two triplets at around δ 2.55 & 3.53 (-CH_2-CH_2-); signals in the region δ 6.5-7.9 (aryl protons).

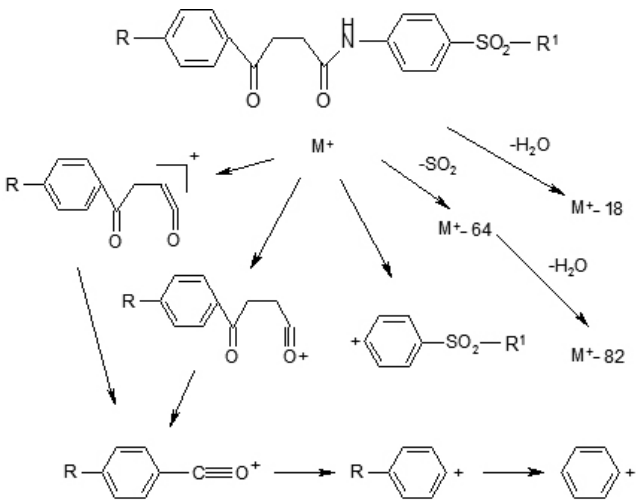


Chart 1. Proposed Mass fragmentation pattern of the synthesized amides.

The mass spectra showed molecular ion peaks in reasonable intensities supporting the structure. The following points could be made regarding the mass fragmentation pattern of compounds **5-l4**: There was splitting of Ar-$COCH_2CH_2$-CON-bond resulting in formation of Ar-$COCH_2CH_2$-C$^oO^+$ (fragment-1) or [Ar-$COCH_2CH$=C=O]$^+$ (fragment-2) and/or R''-SO_2-Ph^+. The fragment-1/2 and the fragment R''-SO_2-Ph^+, could be important for diagnosis of successful formation of the product, found correspondent to their parent 3-aroylpropionic acid moiety and sulphonamide moiety, respectively. Fragment-1/2 further splitted to Ar-C$^oO^+$ and to Ar^+ and then to $C_6H_5^+$ (m/z=77). In some cases, there was 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 proposed fragmentation pattern is presented in **Chart 1**.

Biological evaluation

Antiinflammatory activity

The in-vivo antiinflammatory activity of the synthesized compounds **5-14** was evaluated at 10 mg/kg oral dose and compared with the standard drug indomethacin at the same oral dose. The obtained results revealed that two compounds, **6** and **9** which showed 54.56% and 51.81% inhibition, respectively, were good in their antiinflammatory action and their activity was comparable to that of the standard drug indomethacin (66.24%) at the same dose level. Another compound, compound **10** showed significant activity with 47.13% inhibition (Table 1).

Results indicate that compounds having chlorobenzoyl propanoic acid and/or sulfamethoxazole moiety as promoiety have high degree of activity.

Acute Ulcerogenesis

The synthesized amides 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 0.42 to 1.33, whereas the standard drug indomethacin showed high severity index, 2.25 (Table 1). All the tested compounds exhibited better gastro-intestinal profile as compared to the standard drug indomethacin.

Antibacterial activity

The compounds **5-14** were evaluated for their antibacterial activity 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[12]. Ciprofloxacin was used as standard drug for comparison, which showed *MIC*-6.25 mg/mL against all the three bacterial strains. The compounds **7** showed very good activity against *S. aureus* and *E. coli* with *MIC* 12.5 µg/mL. Similar type of activity was shown by the compounds **5** against *S. aureus* and *P. aurogenosa* at 12.5 µg/mL concentration. Compounds **5** and **8** showed significant activity against *E. coli* with *MIC* 25.0 µg/mL. Compounds **7** was good in its action against *P. aurogenosa* with *MIC* 25.0 µg/mL. Other compounds were moderate in their action. From the antibacterial results, it was observed that the compound derived from chlorobenzoyl propionic acid were active among the tested compounds (Table 1).

Table 1. Biological activity data of the title compounds.

Compound	Antiinflammatory activity (% inhibition ± S.E.M.)[a]		Ulcerogenic activity (severity index ± S.E.M.)[a]	Antibacterial activity (*Minimum Inhibitory Concentration*)		
	After 2 hr	After 3 hr		*S. aureus*	*E. coli*	*P. aurogenosa*
Control	-	-	0.00	-	-	-
Indomethacin	52.01±4.27	66.24± 2.1	2.25±0.21			
Ciprofloxacin				6.25	6.25	6.25
5	21.02±2.56**	34.82±1.59**	0.75±0.28**	12.5	25	12.5
6	47.13±4.06	54.56±2.10**	1.00±0.29**	50	50	>100
7	24.42±1.69**	27.60±1.96**	0.67±0.21**	12.5	12.5	25
8	14.23±1.53**	18.89±1.70**	0.58±0.20**	50	25	50
9	40.97±2.22*	51.81±1.84**	1.33.±0.33*	>100	>100	>100
10	21.23±1.96**	47.13±2.96**	0.75±0.11**	>100	>100	>100
11	35.03±3.40**	40.76±1.79**	0.83±0.21**	>100	>100	>100
12	16.14±1.87**	31.00±2.45**	0.42±0.15**	50	>100	50
13	32.06±2.49**	43.52±3.06**	0.83±0.17**	50	>100	>100
14	10.40±2.05**	11.68±1.12**	0.58±0.15**	>100	>100	>100

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

CONCLUSIONS

As concluding remarks we obtained herein two new compounds (**6** & **9**) 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 **5** and **7** showed significant antibacterial activity against the tested microbes with MIC-12.5 mg/mL. These results confirmed the importance of exploring old drugs as safer templates to built new drug candidates.

Acknowledgements: Financial support provided by Department of Science & Technology, New Delhi (SERC-fast track proposal for young scientists), is gratefully acknowledged. We are also thankful to the In-charge, animal house, for providing animals for biological studies and Prof. P.K. Pillai for helping in performing antibacterial activity of the compounds.

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