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Der Pharmacia Lettre, 2016, 8 (7):46-51
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Synthesis and anti-inflammatory activity of some new 4-nitro-2-phenoxymethane sulphonanilide derivatives

Vinit Kumar*, Archana Kapoor and Sunil Kumar

Drug Discovery and Research Laboratory, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar (Haryana), India

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ABSTRACT

*A series of Schiff's bases i.e., N-(4-(benzylideneamino)-2-phenoxyphenyl)-4-methylbenzene-sulfonamide were synthesized from Nimesulide and studied for their in vivo anti-inflammatory activity. Hydrolysis of Nimesulide with sulphuric acid led to the formation **1** which on further reaction with benzene sulphonyl chloride yielded the title compounds **2.** Compounds **2** reduced with tin in presence of con. HCl yielded compound **3** which further refluxed with different benzaldehyde in presence of ethanol for synthesis of Schiff's bases of Nimesulide. All the synthesized derivatives were characterized with FTIR and NMR spectral analysis and evaluated for their anti-inflammatory activity in-vivo.*

Keywords: Nimesulide, Schiff's base, anti-inflammatory, %inhibition of paw volume.

INTRODUCTION

Inflammation is a series of events in response to injury to facilitate repair and return the tissue to normal function. Inflammation is initiated by many factors (such as physical damage, mechanical trauma, irradiation, heat, chemicals, infections etc.), these factors known as stimulus of inflammation [1]. It can be classified into two types- Acute and Chronic [2].Nimesulide, (4-nitro-2-phenoxymethanesulphonanilide) is a non-carboxylic acid COX-2 selective inhibitor that belongs to sulphonanilide family of non-steroidal anti-inflammatory drugs [3] with one hydrogen bond donor and six hydrogen bond acceptors. It was discovered by Dr. George (GGI) and their colleagues at Riker Laboratories Inc. (later the part of 3M Company at St Paul, Minnesota, US) [4]. It has high gastro tolerability as compare to other agents of this class [5].It also acts as gastro-protective agent [3]. It has been found that it also shows anticancer activity for chemically induced carcinogenesis in rats. It has been found that Nimesulide active in colon, lung [6], mammary, tongue and urinary bladder cancer [7].The synthesized compounds were characterized on the basis of IR and 1H NMR spectral data. All the compounds were screened for their *in vivo* anti-inflammatory activity and %inhibition of paw volume was calculated.

MATERIALS AND METHODS

Chemistry

All the chemicals and reagents were of analytical grade and were used without further purification. Melting points were determined by capillary tube method and are uncorrected. All the reactions and purity of synthesized compounds was deduced by thin layer chromatography (TLC) using silica-G plate. The plates were developed by exposing to the iodine vapours. Infrared spectra were recorded by Perkin Elmer spectrophotometer using KBr

pellets. Proton nuclear magnetic resonance spectra (1H NMR) were recorded on BRUKER AVANCE II 400 NMR spectrophotometer. Chemical shifts are expressed as δ values (ppm) downfield using tetramethyl silane as internal standard.

Synthesis of 4-nitro-2-phenoxyaniline (1)
Nimesulide (2g, 0.0064mole) was mixed with sulphuric acid (3.5ml of 80% of sulphuric acid) in a conical flask and heated on hot plate at 110-115◦C until a clear solution obtained (2-5 minutes). Temperature measured with help of thermometer. Reaction mixture allowed to cool and poured into 25-30ml of water. Resulting solution made alkaline with 20% sodium hydroxide solution. Solids of 4-nitro-2-phenoxyaniline separated via filtration. A yellow colored product was obtained which was recrystallized with ethanol [8].

Synthesis of N-(4-nitro-2-phenoxyphenyl)benzenesulfonamide (2)
4-Nitro-2-phenoxyaniline (1g, 0.0043 mole) was refluxed with benzene sulphonyl chloride (2g, 0.014 mole) for 30 minutes. After completion of reaction, reaction mixture was poured into 10ml of cold water and stirred until the product crystalized. Filtered off the solids and recrystallized from ethanol [9].

Synthesis of N-(4-amino-2-phenoxyphenyl)benzenesulfonamide (3)
N-(4-nitro-2-phenoxyphenyl)benzenesulfonamide (1g, 0.0026 mole) was added in a mixture of tin (0.6g, 0.005 mole) and 20ml of conc. HCl. The resultant mixture was heated on water bath at 90◦C for 3 hr. after completion of reaction the mixture was poured into ice water which resulted in formation of solids. The solid separated via filtration. After basification the crude product obtained was purified by recrystallization from methanol [10].

Synthesis of N-(4-(benzylideneamino)-2-phenoxyphenyl)-4-methylbenzene-sulfonamide (4)
N-(4-amino-2-phenoxyphenyl)benzenesulfonamide (1g, 0.003mol) and substituted benzaldehyde (0.32g, 0.003mol) were mixed with ethanol in a 250 ml round bottom flask and few drops of glacial acetic acid were added. Reaction mixture was refluxed for 4 h. The reaction mixture was cooled in ice-bath and the precipitated solid was filtered through a funnel. The crude product was further purified by recrystallization from ethanol [11].

Table 1. Physicochemical characterization of Nimesulide derivatives

Compound	Molecular Formula	Molecular Weight	Melting Point(◦C)	R_f Value	% Yeild
N-1	$C_{25}H_{19}ClN_2O_3S$	462.95	168-172	0.70	75.21
N-2	$C_{25}H_{19}ClN_2O_3S$	462.95	169-174	0.71	74.20
N-3	$C_{25}H_{19}BrN_2O_3S$	507.4	166-170	0.72	72.15
N-4	$C_{25}H_{19}BrN_2O_3S$	507.4	160-164	0.73	71.80
N-5	$C_{26}H_{22}N_2O_3S$	442.53	170-175	0.68	68.71
N-6	$C_{26}H_{22}N_2O_4S$	458.53	161-165	0.66	68.59
N-7	$C_{27}H_{25}N_3O_3S$	471.57	172-176	0.75	70.54
N-8	$C_{25}H_{20}N_2O_4S$	444.5	165-170	0.80	73.40
N-9	$C_{25}H_{20}N_2O_4S$	444.5	175-179	0.81	69.30
N-10	$C_{25}H_{20}N_2O_3S$	428.5	162-167	0.69	68.50

Spectral data of the title compounds
N-(4-(2'-chlorobenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-1).
IR (KBr, cm^{-1}): 3415.54 (N-H str), 1592.52 (C=C aromatic), 1259.54 (C-N st.), 1312.54 (C-O *str.*), 1154.45 (S=O gp), 1654.83 (C=N, azomethine), 659.50 (C-Cl *str.*); ^{1}H NMR DMSO, δ (ppm): 4.24 (1H, br (S), NH), 6.4-6.74 (3H, m, 1,2,4), 7.0-7.06 (3H, m, 9, 11 ,13), 7.23-7.93 (11H, m, aromatic), 8.36 (1H, s, H of CH=N).

N-(4-(4'-chlorobenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-2).
IR (KBr, cm^{-1}): 3405.41 (N-H str), 1585.45 (C=C aromatic), 1251.68 (C-N st.), 1308.10 (C-O), 1148.54 (S=O gp), 1624.23 (C=N, azomethine), 651.50 (C-Cl *str.*); ^{1}H NMR DMSO, δ (ppm): 4.25 (1H, br (S), NH), 6.42-6.74 (3H, m, 1,2,4), 6.94-6.98 (3H, m, 9, 11 ,13), 7.30-7.85 (11H, m, aromatic), 8.29 (1H, s, H of CH=N).

N-(4-(2'-bromobenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-3).
IR (KBr, cm^{-1}): 3389.21 (N-H str), 1586.83 (C=C aromatic), 1246.32 (C-N st.), 1302.23 (C-O *str.*), 1145.25 (S=O gp), 1632.53 (C=N, azomethine), 685.30 (C-Br *str.*); ^{1}H NMR DMSO, δ (ppm): 4.34 (1H, br (S), NH), 6.45-6.75 (3H, m, 1,2,4), 6.98-7.04 (3H, m, 9, 11 ,13), 7.22-7.54 (11H, m, aromatic), 8.38 (1H, s, H of CH=N).

***N*-(4-(4'-bromobenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-4).**
IR (KBr, cm^{-1}): 3398.32 (N-H str), 1590.53 (C=C aromatic), 1245.52 (C-N st.), 1310.10 (C-O), 1150.41 (S=O gp), 1620.23 (C=N, azomethine), 675.30 (C-Br *str*.). ^{1}H NMR DMSO, δ (ppm): 4.46 (1H, br (S), NH), 6.53-6.68 (3H, m, 1,2,4), 7.02-7.11 (3H, m, 9, 11 ,13), 7.24-7.68 (11H, m, aromatic), 8.12 (1H, s, H of CH=N)

N-(4-(4'-methylbenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-5).
IR (KBr, cm^{-1}): 3386.54 (N-H str), 1582.30 (C=C aromatic), 1384.42 (CH_3 bend), 1249.45 (C-N st.), 1308.15 (C-O *str*.), 1126.52 (S=O gp), 1630.23 (C=N, azomethine). ^{1}H NMR DMSO, δ (ppm): 4.26 (1H, br (S), NH), 6.58-6.69 (3H, m, 1,2,4), 6.98-7.06 (3H, m, 9, 11 ,13), 7.22-7.62 (11H, m, aromatic), 8.39 (1H, s, H of CH=N), 2.21 (3H, s, CH_3)

N-(4-(4'-methoxybenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-6).
IR (KBr, cm^{-1}): 3401.54 (N-H str), 1578.20 (C=C aromatic), 1251.26 (C-N st.), 1310.21 (C-O *str*.), 1135.45 (S=O gp), 1624.36 (C=N, azomethine). ^{1}H NMR DMSO, δ (ppm): 4.28 (1H, br (S), NH), 6.68-6.72 (3H, m, 1,2,4), 6.95-7.06 (3H, m, 9, 11 ,13), 7.20-7.59 (11H, m, aromatic), 8.38 (1H, s, H of CH=N), 3.93(3H, s, OCH_3).

N-(4-(4'-N',N'-dimethylaminobenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-7).
IR (KBr, cm^{-1}): 3410.12 (N-H *str*.), 1565.15 (C=C aromatic), 1249.40 (C-N *str*.), 1298.51 (C-O *str*.), 1142.20 (S=O gp), 1620.40 (C=N, azomethine). ^{1}H NMR DMSO, δ (ppm): 4.46 (1H, br (S), NH), 6.65-6.74 (3H, m, 1,2,4), 6.98-7.10 (3H, m, 9, 11 ,13), 7.22-7.59 (11H, m, aromatic), 8.38 (1H, s, H of CH=N), 3.1 (6H, s, $-N(CH_3)_2$)

N-(4-(2'-hydroxybenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-8).
IR (KBr, cm^{-1}): 3721.54 (OH *str*.), 3401.54 (N-H str), 1578.20 (C=C aromatic), 1251.26 (C-N st.), 1310.21 (C-O *str*.), 1135.45 (S=O gp), 1624.36 (C=N, azomethine) ^{1}H NMR DMSO, δ (ppm): 4.51 (1H, br (S), NH), 6.54-6.69 (3H, m, 1,2,4), 6.96-7.05 (3H, m, 9, 11 ,13), 7.25-7.68 (11H, m, aromatic), 8.31 (1H, s, H of CH=N), 4.5 (1H, s, OH).

N-(4-(4'-hydroxybenzylideneamino)-2-phenoxyphenyl) benzenesulfonamide (N-9).
IR (KBr, cm^{-1}): 3747 (OH *str*.), 3401.54 (N-H *str*.), 1578.20 (C=C aromatic), 1251.26 (C-N st.), 1310.21 (C-O *str*.), 1135.45 (S=O gp), 1624.36 (C=N, azomethine); ^{1}H NMR DMSO, δ (ppm): 4.24 (1H, br (S), NH), 6.38-6.72 (3H, m, 1,2,4), 7.04-7.10 (3H, m, 9, 11 ,13), 7.3-7.90 (11H, m, aromatic), 8.36 (1H, s, 23); 5.2 (1H, s, OH)

N-(4-(benzylideneamino)-2-phenoxyphenyl)benzenesulfonamide (N-10).
IR (KBr, cm^{-1}): 3385.32 (N-H str), 1585.53 (C=C aromatic), 1254.52 (C-N st.), 1312.10 (C-O), 1145.41 (S=O gp), 1620.23 (C=N, azomethine). ^{1}H NMR DMSO, δ (ppm): 4.51 (1H, br (S), NH), 6.64-6.71 (3H, m, 1,2,4), 6.99-7.08 (3H, m, 9, 11 ,13), 7.23-7.63 (12H, m, aromatic), 8.23 (1H, s, 23)

Anti-inflammatory activity
Carrageenan induced acute paw edema model-
Albino wistar rats (160-220g) were challenged against test compounds for anti-inflammatory activity. Nimesulide was used as standard. 0.1ml of a 1% solution of carrageenan in 0.9%w/v saline is injected subcutaneously into the plantar region of the left hind paw after 30min. of test drug administration. Test drug (100mg/kg) administered orally. Carrageenan injected and control paw volumes are measured as required from 0.5-3hrs [12].

% inhibition calculated by the formula:

% inhibition = $(1-V_t/V_c)*100$

Where V_t is the mean increase in the paw volume in the test animal group
V_c is the mean increase in the paw volume in the control group

Table 2. Anti-inflammatory activity (Paw volume)

Compound	Paw volume (mean ±S.E.M)				
	0 min	30 min	60 min	120 min	180 min
Control	1.160±0.03	1.451±0.038	1.682±0.04	1.852±0.03	1.886±0.05
Nimesulide	1.020±0.03	1.215±0.02**	1.285±0.04**	1.348±0.03**	1.321±0.02**
N-1	1.053±0.03	1.291±0.03*	1.413±0.02**	1.491±0.03**	1.548±0.04**
N-2	1.082±0.04	1.282±0.04*	1.373±0.02**	1.448±0.02**	1.419±0.03**
N-3	1.143±0.02	1.320±0.02	1.397±0.02**	1.504±0.04**	1.520±0.04**
N-4	1.151±0.04	1.287±0.03*	1.392±0.03**	1.464±0.02**	1.458±0.03**
N-5	1.113±0.02	1.331±0.03	1.514±0.03*	1.641±0.02**	1.672±0.04**
N-6	1.113±0.04	1.341±0.03	1.510±0.04*	1.626±0.03**	1.632±0.02**
N-7	1.104±0.03	1.360±0.04	1.537±0.02	1.678±0.03*	1.716±0.03*
N-8	1.141±0.03	1.334±0.03	1.530±0.03*	1.584±0.02**	1.650±0.03**
N-9	1.076±0.04	1.332±0.02	1.463±0.03**	1.558±0.03**	1.565±0.03**
N-10	1.092±0.04	1.244±0.02**	1.329±0.04**	1.389±0.03**	1.392±0.02**

** denotes p<0.05 as compared to control group,* ******** *denotes p<0.01 as compared to control group. Values are expressed as mean ±SEM (n=6), One way ANOVA followed by Dunnett's t- test.*

Table 3. Percentage inhibition of paw volume

Compound	%inhibition of paw volume			
	30 min	60 min	120 min	180 min
Nimesulide	16.26	23.60	27.18	29.92
N-1	11.02	15.97	19.47	17.87
N-2	11.64	18.35	21.78	24.72
N-3	8.98	16.89	18.77	19.37
N-4	11.30	17.24	20.94	22.69
N-5	8.25	9.98	11.34	11.30
N-6	7.53	10.17	12.19	13.43
N-7	6.23	8.62	9.37	8.98
N-8	8.01	11.41	14.46	12.48
N-9	8.16	12.97	15.87	16.97
N-10	14.23	20.93	24.97	26.14

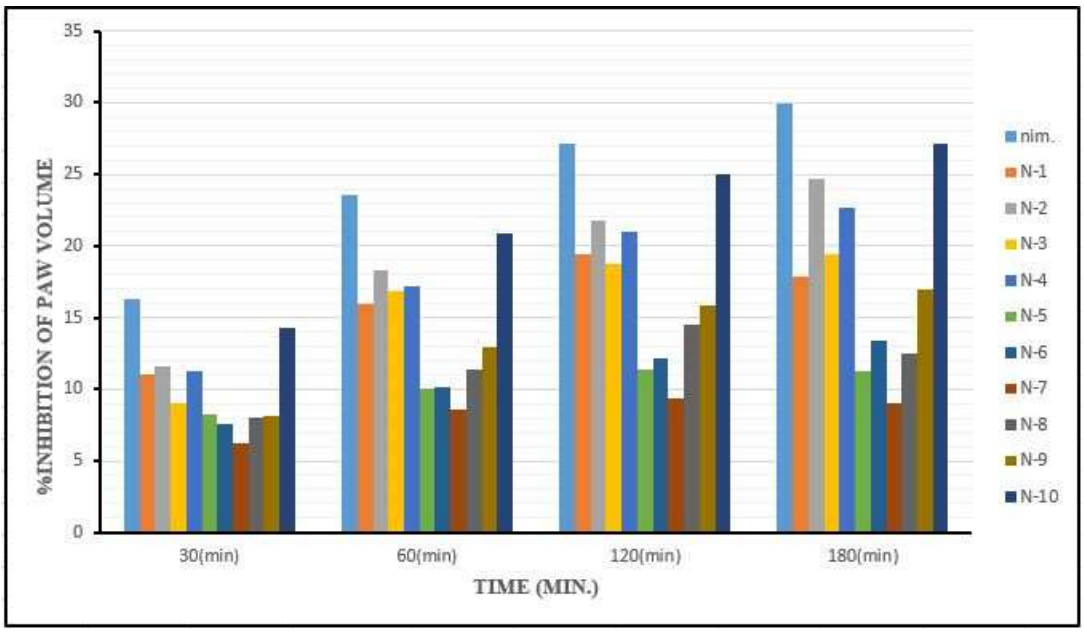
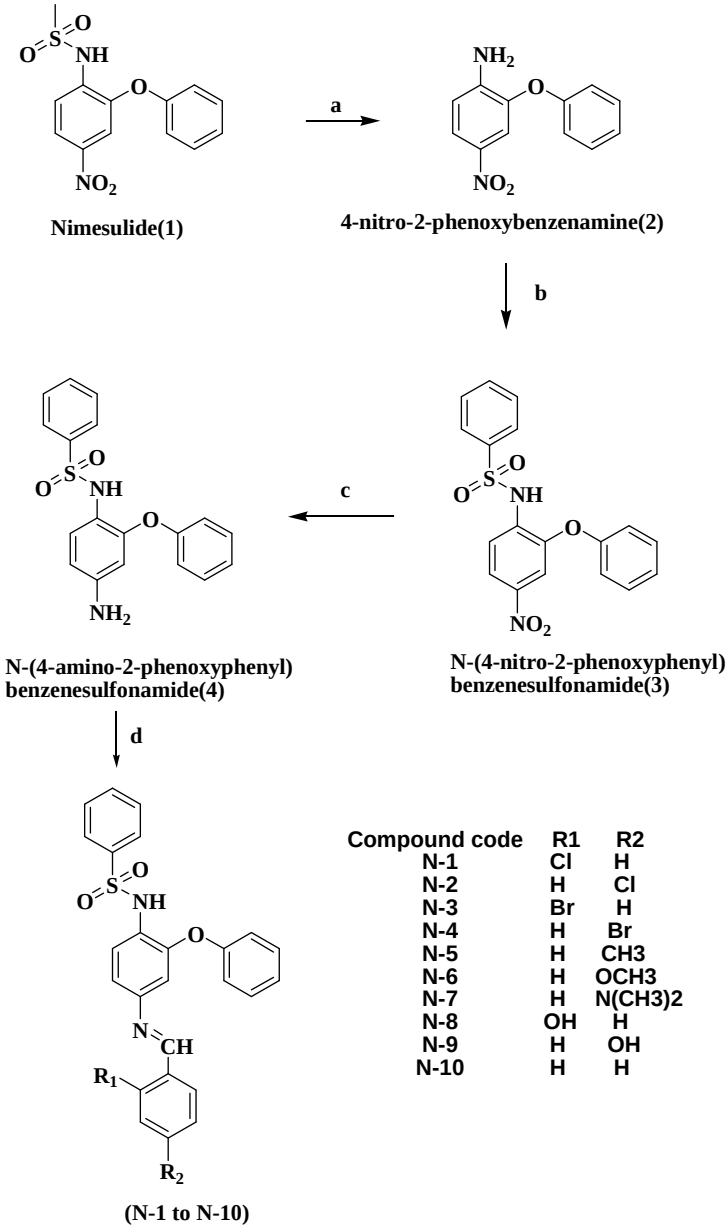


Fig 1. %Inhibition of Nimesulide derivatives

RESULTS AND DISCUSSION

Chemistry

Scheme 1 was followed for synthesis of Nimesulide derivatives. Hydrolysis of Nimesulide gave compound **1** which further reacted with benzene sulphonyl chloride to yielded compound **2**. On reduction of compound **2** with tin in presence of con. HCl yielded compound **3** which further reacted with different benzaldehyde to synthesize Schiff's bases of Nimesulide. All the compounds were synthesized in good yield. All the compounds were characterized by FTIR and ^{1}H NMR spectra.



Compound code	R1	R2
N-1	Cl	H
N-2	H	Cl
N-3	Br	H
N-4	H	Br
N-5	H	CH3
N-6	H	OCH3
N-7	H	N(CH3)2
N-8	OH	H
N-9	H	OH
N-10	H	H

Reagents and conditions- (a) 80%sulphuric acid,heat for 2-5min.(b)Benzenesulphonyl chloride, pyridine and reflux for 30min. (c) Tin,conc.HCl and reflux for 3hrs (d)Substituted benzaldehyde,ethanol, few drops of glacial acetic acid, reflux for 4hrs

Anti-inflammatory activity

All the synthesized title compounds were screened for their *in vivo* anti-inflammatory activity and %inhibition of paw volume was determined. From observations it was found that compounds **N-2, N-4** and **N-10** showed the percentage inhibition of 24.72%, 22.69% and 26.14% respectively after 3 hours. These three compounds are the most relatively potent of all the compounds tested for anti-inflammatory activity. The compounds **N-1, N-3** and **N-9** showed moderate anti-inflammatory activity with percentage inhibition of 17.87%, 19.37% and 16.97% respectively. The compound **4-N(CH_3)2** showed minimum anti-inflammatory activity with percentage inhibition of 8.98%.

CONCLUSION

Present study describes the synthesis of some new Nimesulide derivatives (Schiff's bases of Nimesulide). Synthesized derivatives were characterized by IR and proton NMR spectra. All the derivatives were evaluated for *in-vivo* anti-inflammatory activity and % inhibition of paw volume was determined. From results, it can be concluded that substitution of electron withdrawing group at ring A increases anti-inflammatory activity whereas electron donating group decreases anti-inflammatory activity. Size of R may also affect anti-inflammatory activity, having a negative effect on anti-inflammatory activity.

Acknowledgements

The authors are thankful to Chairman, Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar (Haryana) India for providing necessary facilities to carry out this work. Our sincere thanks are due to the Co-ordinator, Central Instrument Laboratory, Guru Jambheshwar University of Science and Technology, Hisar (Haryana), India for elemental and spectral analysis.

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