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Synthesis, Characterization and Antimicrobial Activity Studies of 1- and 2-[4-{(4-Chloro phenyl)phenyl methyl}-1-piperazinyl]sulphonyl naphthalenes

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Two isomeric naphthalene sulphonyl compounds *viz.*, 1-and 2-[4-{(4-chloro phenyl)phenyl methyl}-1-piperazinyl] sulphonyl naphthalenes were synthesized from *p*-chloro benzophenone and naphthalene as the main starting materials with piperazine bridge and characterized by spectral methods. Their antimicrobial activities were also studied.

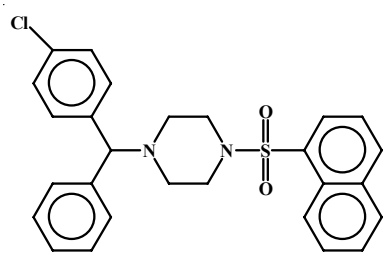
Key Words: Sulphonyl naphthalenes, Piperazine bridged sulphonyl naphthalenes, Antibacterial activity.

INTRODUCTION

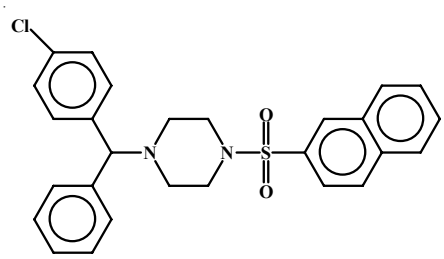
Piperazine derivatives serve as drug intermediates for several drugs. For example, 1-[(4-chlorophenyl)phenylmethyl]piperazine (CPMP) has been prepared[1-3] by different methods and has been used as the key intermediate for the synthesis of cetirizine, a well-known antihistamine drug, which is an ethoxy acetic acid derivative of CPMP.

The same intermediate (CPMP) has been coupled with different moieties to get compounds having antiallergic, antihistamine[4] and antibradykinin[5] properties. For example, CPMP when combined with different saturated or unsaturated monocyclic, bicyclic, tricyclic ketones resulted in the formation of a series of compounds exhibiting stimulation of nerve growth and prevention of neuronal damage[6] caused by neural diseases. From the above visualization and to improve the potential of the bioactivity of the intermediate *viz.*, 1-[(4-chlorophenyl)phenylmethyl] piperazine (CPMP), an attempt was made to convert it into sulfonamide[7], by combining it with an aromatic sulfonyl chloride, because the sulfonamides have been proved to have antiallergic activity [8].

This report is an attempt to synthesize cetirizine like compounds from the intermediate (CPMP) by combining it with α- and β-sulfonyl naphthalene *i.e.*, 1-and 2-[4-{(4-chloro phenyl)phenyl methyl}-1-piperazinyl] sulphonyl naphthalenes (**I** & **II**) since sulfonyl compounds have been demonstrated to be potential sulfa drugs. Hence, such kinds of compounds are expected to have properties common to cetirizine and sulfa drugs.



1-[4-{(4-Chloro phenyl)phenyl methyl}-1-piperazinyl]sulphonyl naphthalene
(**I**)



2-[4-{(4-Chloro phenyl)phenyl methyl}-1-piperazinyl]sulphonyl naphthalene
(**II**)

EXPERIMENTAL

Commercial grade samples of 4-chloro benzophenone and naphthalene, supplied by E. Merck, were used as the primary starting materials for the synthesis of the sulphonyl naphthalenes and all other chemicals used were commercial grade samples obtained from sd-fine chemicals and E. Merck.

Step-1: Preparation of 4-chloro benzhydrol (4-CB)[9,10]: About 5.0 g (0.023 mol) of 4-chloro benzophenone was dissolved in 15 mL of isopropyl alcohol (IPA) and heated to 50ºC followed by the addition of 0.265 g (0.007 mol) of sodium borohydride as a lot with the temperature maintained at 65ºC for 2 h. The reaction mixture was distilled to expel isopropyl alcohol up to 90 %. The resulting solution was cooled and treated with dil HCl (5 mL of conc. HCl in 20 mL of water). Finally the reaction mass was extracted with 15 mL of toluene. The toluene extract was washed with water to pH-7. The compound obtained in this step was taken to next step without isolation but aliquot sample was concentrated, isolated and checked for melting point (m.p. = 58-60ºC).

Step-2: Preparation of 4-chloro benzhydryl chloride (4-CBC)[11]: The 4-chlorobenzhydrol (4-CB) in 15 mL of toluene, obtained from the previous step, was mixed with 10 mL of conc. HCl at 60ºC maintained at the same temperature for 2.5 h. The reaction mixture was cooled to 20ºC to separate into organic and aqueous layers. The toluene layer was washed with 10 % aq. sodium carbonate to pH 7, dried over anhydrous sodium sulphate and taken to next step without isolation.

Step-3: Preparation of 1-[(4-chlorophenyl) phenylmethyl] piperazine. (CPMP)[12,13]: About 0.5 mL of DMF, 0.1 g of KI and 10 g (0.12 mol) of piperazine were mixed with 15 mL of toluene and heated to 80ºC for 0.5 h. This mixture at 80ºC was mixed with 4-CBC in toluene, obtained from step-2 and the temperature was maintained at 80ºC for a period of 2 h followed by refluxing at the same temperature for 12 h. The reaction mixture was then cooled to 20ºC. The toluene layer was washed twice with 20

mL of water and treated with HCl (15 mL conc. HCl in 5mL of water) at 5-10ºC. The reaction mixture was filtered and the aqueous layer was separated from the filtrate. About 10 mL of toluene and 10 mL of methylene dichloride (MDC) washes were given to the aqueous layer and neutralized with 22 mL of 30 % NaOH solution at 10ºC and maintained at 20ºC for 2 h. The solid compound formed was filtered, sucked and dried at 50ºC for 3 h.Yield: 92 %; m.p: 63-65ºC.

Step-4: Preparation of α-sodium naphthalene sulphonate (α-NaNS)[14,15]: About 10 g (0.078 mol) of naphthalene in 11.9 g (0.12 mol) of acetic anhydride was stirred to dissolve at 20ºC and treated with 7.72 g (0.078 mol) of conc. H_2SO_4 dropwise below 25ºC for a period of 3 h and then distilled slowly under vacuum for a period of 1 h at 40ºC. The reaction mass was quenched in lye solution (12 g sodium hydroxide in 50 mL water) at 40-60ºC under stirring. The mass was cooled to 30ºC after 1 h, filtered, bed washed with 30 mL of 1:1 isopropyl alcohol and hexane and dried in vacuum for 6 h at 50ºC. Yield: 85 %.

Step-5: Preparation of α-naphthalene sulphonyl chloride (α-NSC)[16-19]: About 10 g (0.04 mol) of α-NaNS was added to 6.6 g (0.04 mol) of phosphorous oxychloride and heated to 110-115ºC for 3 h. The reaction mixture was cooled to 60ºC, distilled to expel the excess $POCl_3$ and mixed with 40 mL of toluene. The reaction mass further cooled to 20ºC followed by the addition of 20 mL cold water at 20ºC and stirred for 20 min. The toluene layer was washed to pH-7 with water, dried over anhydrous sodium sulphate and distilled out completely under vacuum at 60-65ºC. The compound was purified in 100 mL of hexane. Yield: 50 %; m.p: 69-71.5ºC.

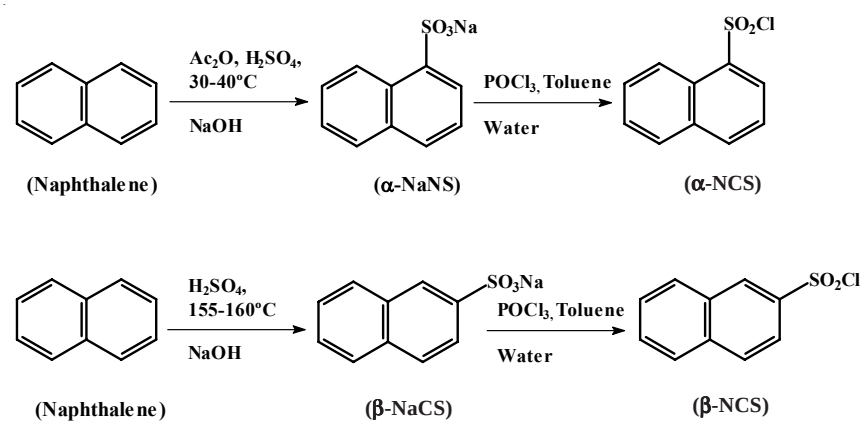
Step-6: Preparation of 1-[4-{(4-chloro phenyl) phenyl methyl}-1-piperazinyl] sulphonyl naphthalene (I): About 5.06 g (0.02 mol) of CPMP and 4 g (0.02 mol) of α-NSC were dissolved in 20 mL of methylene dichloride (MDC) and treated with 2.68 g (0.0265 mol) of triethylamine (TEA), slowly at 20ºC. The reaction mass was warmed to 40ºC and maintained at the same temperature for 4 h. The completion of the reaction was checked by TLC with 1:1 hexane and ethyl acetate mixture as mobile phase. The reaction mixture was cooled to 15ºC and mixed with 50 mL of MDC and 50 mL of water. The MDC layer was separated, washed to neutral pH with 5 % aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was crystallized in 40 mL of isopropyl alcohol. Yield: 59.5 %; m.p: 75-79ºC.

Step-7: Preparation of β-sodium naphthalene sulphonate (β-NaNS): About 2.5 g (0.02 mol) of naphthalene was taken in about 2.0 g (0.02 mol) of sulphuric acid and heated to 165ºC for 15 h. The reaction mass was cooled to 80ºC and quenched over sodium hydroxide solution

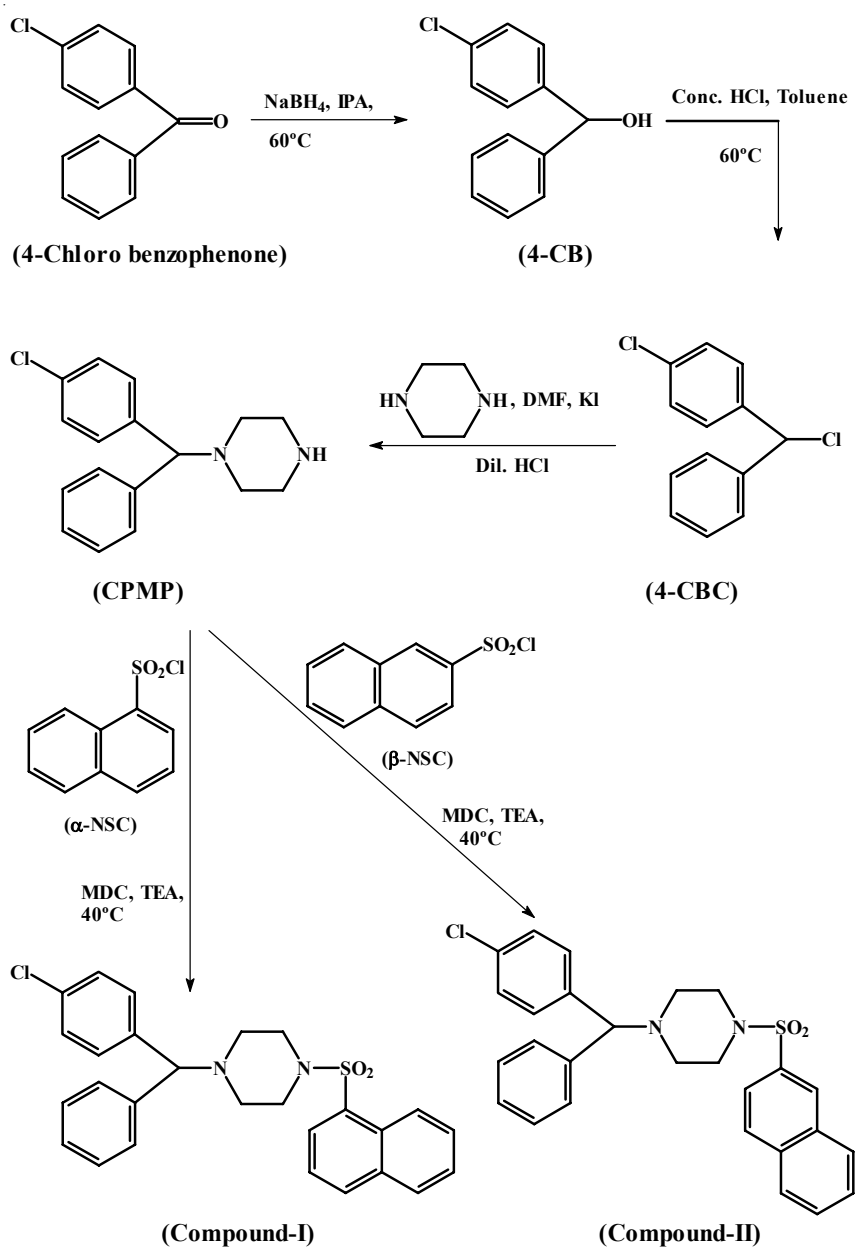
(0.4 mol). The reaction mass was further cooled to 20ºC and filtered. The bed was treated with 50 mL of isopropyl alcohol and 50 mL of hexane. The sodium naphthalene β-sulphonate (β-NaNS) formed was dried under vacuum at 60ºC for 4 h. Yield: 80 %.

Step-8: Preparation of β-naphthalene sulfonyl chloride (β-NSC): About 10 g (0.04 mol) of β-NaNS was added to 6.6 g (0.04 mol) of $POCl_3$ and heated to 110-115ºC for 3 h. The reaction mixture was cooled to 60ºC, distilled out to expel excess $POCl_3$ and mixed with 40 mL of toluene. The reaction mass was further cooled to 20ºC followed by the addition of 20 mL of cold water at 20ºC and stirred for 20 min. The toluene layer was washed to pH-7 with water, dried over anhydrous sodium sulphate and distilled out completely under vacuum at 60-65ºC. The compound was purified in 100 mL of hexane. Yield: 50.8 %; m.p: 74-76ºC.

Step-9: Preparation of 2- [4-{(4-chloro phenyl) phenyl methyl}-1-piperazinyl] sulphonyl naphthalene (II): About 4 g (0.02 mol) of β-NSC and 5.06 g (0.02 mol) of CPMP were dissolved in 20 mL of methylene dichloride (MDC) and treated with 2.68 g (0.027 mol) of triethylamine (TEA), slowly at 20ºC. The reaction mass was warmed to 40ºC and maintained at the same temperature for 4 h. The completion of the reaction was checked by TLC with 1:1 hexane and ethyl acetate as mobile phase. The reaction mixture was cooled to 15ºC and mixed with 50 mL of MDC and 50 mL of water. The MDC layer was separated, washed to neutral pH with 5 % aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was crystallized in 40 mL of isopropyl alcohol. Yield: 59.5 %; m.p: 84-90ºC.



Scheme-I. Preparation on naphthalene sulphonyl chlorides



Scheme-II. Preparation of **I** and **II**

Spectral studies: The mass spectral pattern of the compounds were obtained on a Shimadzu-QP-2010 mass spectrometer, UV-Visible spectra were recorded on LAMBDA-25 spectrophotometer in methanol (2.60×10^{-5} M) using matched quartz cells of path length 1 cm. The IR spectra, in

KBr pellets, were obtained on Perkin Elmer IR Spectrum-1 spectrophotometer and the H^1 & C^{13} NMR spectra, in $CDCl_3$, were recorded using Jeol 300 MHz NMR spectrophotometer.

Antimicrobial activity studies: The antimicrobial activity tests were performed using Bauer[20] disc diffusion method. The test concentrations of the compounds prepared were 0.025 µg/mL in ethyl alcohol. Each disc was impregnated with 25, 50, 75 and 100 µL of the solutions.

The pure cultures were stored in nutrient agar. All the antimicrobial activities were determined by using Mueller Hinton Agar [MHA] (Himedia, Bombay). The MHA plates were prepared by pouring 15 mL of molten medium (pH= 7.2) and allowing it to set for solidification. The 24 h old bacterial cultures were swabbed on the agar plate to form a uniform culture.

Tetracycline (Himedia, Chemical Ltd and Mumbai), served as control. Each concentration was tested in triplicates. The plates were evaluated after incubation at 37ºC for 24 h and the zones of inhibitions were measured at the end of 24 h period.

RESULTS AND DISCUSSION

Mass spectra: Both compounds (I & II) showed the molecular ion peak at m/z = 476 and base peak at m/z = 201 which may arise due to the fission of C-N bond at the chiral carbon producing corresponding secondary carbocation. The intense peak at m/z = 285 and low intense peak at m/z = 191 may arise due to the breakage of N-S bond. The moderate intense peak at m/z = 127 and low intense peak at m/z = 77 may be assigned to naphthalene and phenyl cations respectively.

Electronic spectra: The electronic spectra of compound-**I** showed two prominent peaks in the UV region. The intense high energy absorptions at λ_{max} = 225 nm (C_{max} = 48, 320 M^{-1} cm^{-1}) may be attributed to the allowed $\pi \rightarrow \pi^*$ transition of benzene and naphthalene moieties; whereas, the low intense and low energy transition at λ_{max} = 293 nm (C_{max} = 6,180 M^{-1} cm^{-1}) may be assigned to $n \rightarrow \pi^*$ transitions centered around $-SO_2-$ group.

The electronic spectra of compound-**II** also showed two prominent peaks in the same wave length range in the UV region: The intense high energy absorptions at λ_{max} = 229 nm (C_{max} = 66,420 M^{-1} cm^{-1}) may be attributed to the allowed $\pi \rightarrow \pi^*$ transition of benzene and naphthalene moieties. Another low intense and low energy transition at λ_{max} = 277 nm (C_{max} = 5,350 $M^{-1}cm^{-1}$) may be assigned to $n \rightarrow \pi^*$ transitions centered on $-SO_2-$ group.

IR spectra (KBr): I: Medium intense peaks at 1160 and 1138 cm^{-1} may be attributed to C-N stretching and similar intense peaks at 1592 and 1506 cm^{-1} may be ascribed to aromatic stretching. Absorption at 2813 and 3543 cm^{-1} arises due to N-C-H and $N-CH_2-$ stretching, respectively.

II: The isomer of compound-**I** *viz.*, compound-**II** also showed similar peaks at 1165 and 1132 cm^{-1} (C-N stretching); 1625 and 1590 cm^{-1} (aromatic stretching); 2814 cm^{-1} (N-C-H stretching); 3436 cm^{-1} (N-CH_2-stretching).

NMR spectra ($CDCl_3$): The proton and ^{13}C NMR spectra of the compounds prepared greatly support the structure of the compounds proposed as detailed below.

^{1}H NMR (δ): I: 2.41-2.42 (multiplet, 4H, N-CH_2-CH_2-N); 3.19 (multiplet, 4H, 4H, N-CH_2-CH_2-N); 4.17 (singlet, 1H, Ar-CH-Ar); 7.2-7.25 (multiplet, 9H, Aromatic); 7.53-8.8 (multiplet, 7H, Aromatic).

II: 2.45 (multiplet, 4H, N-CH_2-CH_2-N); 3.08(multiplet, 4H, N-CH_2-CH_2-N); 4.18 (singlet, 1H, Ar-CH-Ar); 7.18-7.24 (multiplet, 9H, Aromatic); 7.62-8.32 (multiplet, 7H, Aromatic).

^{13}C NMR (δ): I: 45.81 (N-CH_2), 51.04 (N-CH_2), 74.88 (Ar-C-Ph), 124.11-134.43 (Aromatic carbons), 140.57 (C-SO_2), 141.38 (C-Cl).

II: 46.33 (N-CH_2), 50.83 (N-CH_2), 74.81 (Ar-C-Ph), 123.15-134.91 (Aromatic carbons), 140.58 (C-SO_2), 141.38 (C-Cl).

Antimicrobial studies: Both compounds (**I** and **II**) were tested for their activities against *Proteus vulgaris*, *Proteus mirabilis*, *Escherchina coli* and *Pseudomonas aureginosa* at different concentrations of the compounds. Both compounds are found to be active against *Proteus vulgaris* only. Compound **II** *viz.*, 2-[4-{(4-chloro phenyl) phenyl methyl}-1-piperazinyl]sulphonyl naphthalene is found to be more active even at low concentration than compound **I** *viz.*, 1-[4-{(4-Chloro phenyl) phenyl methyl}-1-piperazinyl] sulphonyl naphthalene, the latter being active only at moderately higher concentrations.

TABLE-1
ANTIBACTERIAL ACTIVITY OF 1- AND 2-[4-{(4-CHLORO PHENYL) PHENYL METHYL}-1-PIPERAZINYL]SULPHONYL NAPHTHALENES (**I** and **II**) AGAINST *Proteus vulgaris* ZONE OF INHIBITION [DIAMETER (mm)]

Compound	*Volume of the solution used (µL)			
	25	50	75	100
I	-	-	2	5
II	2	4	6	8
Tetracycline	4	10	13	15

*Concentration of the solution prepared: 0.025 µg/mL; No activity (-).

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