IJBPAS, June, 2022, 11(6): 2698-2705

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

SYNTHESIS AND CHARACTERIZATION OF NOVEL NAPHTHALENE SUBSTITUTED SULPHONAMIDE DERIVATIVE

K. N. RAJINI KANTH, RAMA RAO NADENDLA, T. NITHISH BABU, S. SHALEMRAJU, P. N. MANI EASWAR, K. MANOJ KUMAR AND T. RAVI TEJA

Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur-522034

*Corresponding Author: Prof. K. N. Rajini Kanth: knrkanth2009@gmail.com

Received 20th June 2021; Revised 20th Aug. 2021; Accepted 28th Sept. 2021; Available online 1st June 2022

https://doi.org/10.31032/IJBPAS/2022/11.6.6160

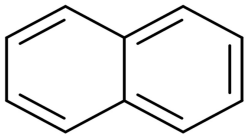
ABSTRACT

Most of the naphthalene substituted compounds are used as antimicrobial agents, anti-mycobacterial agents, nasal decongestants and anti-inflammatory agents. In the present work the synthesis and characterization of novel sulfonamide derivative by incorporating the naphthalene containing moiety as a substituent was carried out. Compound was synthesized initially by bromination of 1-Hydroxy acetonaphthone by using N-bromosuccinimide, followed by the reaction of obtained intermediate with sulphanilamide at low temperature. The final compound was characterized by IR, NMR and Mass spectrometric techniques. The results have shown the presence of characteristic groups. By interpreting spectral data, we have predicted that the final product was obtained. Considering the importance of naphthalene substituted sulpha derivatives in medicine, we would like to proceed for screening of biological activities.

Keywords: 1-Hydroxy acetonaphthone, N-bromosuccinimide, Sulphanilamide, Spectral interpretation

INTRODUCTION

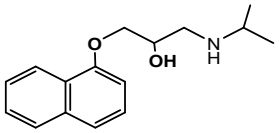
The discovery, development and identification of biologically active anti-bacterial agents have gained a lot of importance in recent years, even though there is considerable number of side effects. There is a need to develop new anti-bacterial agents with minimum side effects.



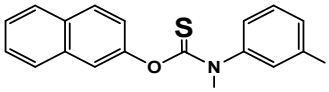
Napthalene

Naphthalene is an anti-microbial agent and a key member of this arena class, in which two benzene rings are fused in ortho positions. Naphthalene is a colorless solid with a flaked-crystal appearance and a melting point of 82.2o C. It has been successful. Mothballs have a distinct odour. It's highly flammable and steadily sublimes at room temperature. Naphthalene is Water insoluble, moderately soluble in alcohol, and very soluble in ether and benzene. The aromatic electrophilic substitution reaction occurs with naphthalene. [1] Our objective of this research is to synthesize substituted naphthalene derivatives based on experimental procedure reported for similar set of compounds in the literature. To characterize the synthesized compounds Infrared spectroscopy, NMR spectroscopy, and Mass spectrometric techniques.

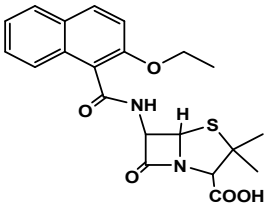
S. No.	Drug	Target	MOA	Clinical Uses
1	Propranolol[2]	β_1, β_2 Receptors	It is non selectively blocking the β-receptors.	It helps in the treatment of hypertension and migraine.
2	Menadione[3]	Co-factors	It acts as a vitamin K analogue, acting as Co-factor in the synthesis of factors II, VII, IX, X in liver.	Nutritional supplements and treatment of hypoprothrombinemia.
3	Naproxen[2]	CoX Enzymes.	It inhibits the CoX-I and CoX-II, thereby inhibits the prostaglandins	Anti-inflammatory, Treatment of Arthritis, Rheumatoid Arthritis, Osteoarthritis.
4	Nafcillin[2]	Penicillin binding protein 3 & 1A	It inhibits the cell wall synthesis by inhibiting the peptidoglycan synthesis	Treatment of infections caused by streptococcus species.
5	Naphazoline[4]	α_1 receptors	It acts as α_1-agonist by the release of Nor-epinephrine in sympathetic nerves binds to α_1 receptors and causes vasoconstriction.	Nasal decongestant.
6	Naftopidil[5]	α_{1A} receptors	α_{1A} receptor antagonist and blocks α_{1D} receptors	Treatment of lower UTI and Benign prostate hyperplasia.
7	Nafamostat[4]	Tryptase enzyme	It inhibits the Tryptase enzyme	To treat the acute Pancreatitis and may effectively blocks the viral entry process.
8	Tolnaftate[2]	Squalene epoxidase enzyme	It inhibits the activity of Squalene epoxidase enzyme that is essential in the formation of sterols necessary for fungal cell membrane.	To treat fungal infections such as Ring worm, Athletes foot.
9	Terbinafine[2]			
10	Butenafine[2]			
11	Naftifine[2]			It has Triple action Anti-Fungal, Anti-bacteria; Anti-Inflammatory.



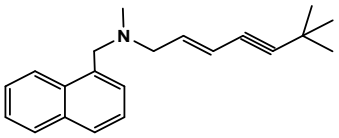
Propranolol[2]



Tolnaftate[2]



Nafcillin[2]



Terbinafin[2]

MATERIALS AND METHODOLOGY

All the chemicals and apparatus that are used for the synthesis were procured from the National Scientific Products (Guntur), Chalapathi Institute of Pharmaceutical Sciences (Guntur). The reaction completion was monitored by melting points. IH Nuclear Magnetic resonance (1H NMR) Bruker Avance II400 MHz NMR spectrophotometer using appropriate deuterated solvents and expressed in parts per million (δ, ppm) from methanol (internal standard). Infrared (IR) spectra were recorded on a Bruker IR affinity FTIR spectrophotometer using KBr pellet method.

I. SYNTHESIS OF 1-HYDROXY-2-ACETONAPHTHONE:

Zinc chloride (7.5g) is weighed and added in hot glacial acetic acid (20ml) which is taken in RB flask and set for refluxation until the compound is completely dissolved. Later 1.5g of 1- Naphthol was added and set for refluxation for 8hrs (Parallel synthesizer).The formed product is cooled and washed with acidified water and dried.

II.SYNTHESIS OF N-BROMOSUCCINIMDE:

To the mixture of 0.016mol (0.64g) sodium hydroxide,300g Crushed ice and 400ml water,0.0162 mol(1.60g) succinimide is added and dissolved. Cool the mixture and 0.85ml (0.0165mol, 2.64g) Bromine at once by constant stirring. Filter and collect the precipitate thus obtained.

III. SYNTHESIS OF 2-BROMO-1-(1-HYDROXYNAPHTHALENE-2-YL) ETHANONE:

0.01 moles (1.86g) of 1-hydroxy acetonaphthone is taken in an RB flask which is packed with 10%w/w silica gel (120mg). Set it for refluxation. Add the N-Bromosuccinimide (2136mg, 12mmol) in 6 portions (356mg) and add methanol 10ml into RB flask and set it for refluxation 10-

15mins until the complete disappearance of substrate. The filtrate was concentrated under the vacuum with double distilled water and quenched with an aqueous Sodium thiosulphate and product extracted with Dichloromethane.

IV SYNTHESIS OF SULPHANILIMDE:

a) Synthesis of p-Acetamido benzene sulphonyl chloride:

Dry acetanilide (2.7g) is placed in a clear, dry 50ml RB flask chlorosulfonic acid (8.0 ml) is added. The reaction flask is cooled in a cool water bath maintained between 10 to 15 °C. Chlorosulfonic acid is rapidly all at once through the dropping funnel. The solution is rapidly stirred keeping it in the cooling water bath with at temperature below 20 °C. The reaction mixture is transferred into 250ml beaker containing 150g of crushed ice. The ice slurry is stirred using a stir rod. The precipitate is collected by vacuum filtration and washed with 15ml portions of cold water until the filtrate tests neutral to pH paper. The product is air dried on the filter funnel by pulling air through for at-least 10min. The product is used immediately for synthesis of 4-acetamido benzene sulfonamide.

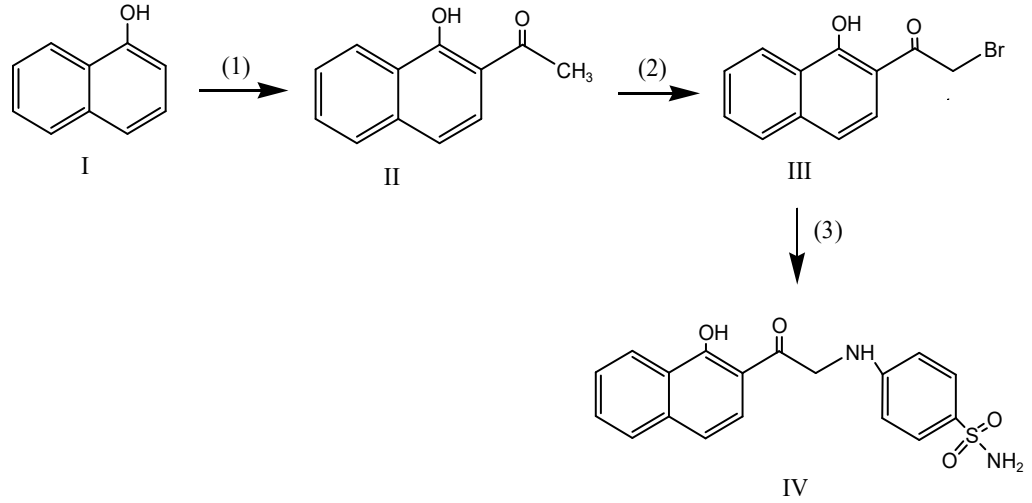
b) Synthesis of p-Acetamido benzene sulfonamide:

Transfer the crude p-Acetamido benzene sulphonyl chloride into a 100ml RB flask. Add gradually mixture of 20ml of concentrated ammonia and 20ml of water. Mix the contents of flask thoroughly and heat the mixture with occasional stirring for about 10 mins. The sulphonyl chloride derivative is converted to pasty suspension of corresponding sulfonamide. Cool the suspension in ice and add dilute sulphuric acid until the mixture is just acidic to litmus paper, collect the product under Buchner funnel, wash with cold water and dry in hot air oven at a temperature of 100^0c for 15 mins.

c) Synthesis of p-Amino benzene sulfonamide (Sulphanilamide):

Transfer the crude p-Acetamido benzene sulfonamide into a 100ml RB flask. Add 5 ml of concentrated HCl and add 15 ml of distilled water. Boil the mixture gentle under reflux for 60 mins. The solution when cooled to a room temperature, should deposit no solid amide. If the solid separates, heat further for 15-20 mins. Cool the solution, add 1g of decolorizing carbon, heat the mixture to boil and filter. Place the filtrate in 250ml beaker and cautiously add 4g of solid sodium bicarbonate in portions with stirring. Check the pH of the reaction mixture with litmus paper (Neutral pH should be obtained). Cool the solution in ice and filter off the Sulphanilamide at pump. The crude product of Sulphanilamide was recrystallized with alcohol. Melting point of sulfanilamide is 168-170^0c.

V) SYNTHESIS OF 4-((2-(1-HYDROXYNAPHTHALEN-2-YL)-2-OXOETHYL) AMINO) BENZENE SULFONAMIDE: 0.01moles of 2-bromo-1-(1-hydroxynaphthalen-2-yl) ethanone is dissolved in dimethyl sulfoxide. Separately 0.01moles of Sulphanilamide is dissolved in dimethyl sulfoxide. Then both are added in to prechilled china dish maintaining the temperature of 0-5 degrees centigrade. Keep it aside for few hours (3-4), after that solution is transferred into 150 gm crushed ice with simultaneous stirring. Precipitate was separated through vaccum filtration. Crude product was recrystallized with alcohol.



Scheme: Synthetic route followed for the synthesis of Naphthalene substituted Sulfonamide derivatives. (1) $Zncl_2$/GAA; (2) N-bromosuccinimide, SiO_2, Methanol; (3) Sulphanilamide, 5-10^oC, DMSO. (I) 1-Napthol, (II) 1-Hydroxyacetonapthone, (III) 2-bromo-1-(1-hydroxynaphthalene-2-yl) ethanone, (IV) 4-((2-(1-hydroxynaphthalen-2-yl)-2-oxoethyl)amino)benzene sulfonamide

RESULTS & DISCUSSION

CHARACTERIZATION OF 4-((2-(1-HYDROXYNAPHTHALEN-2-YL)-2-OXOETHYL)AMINO)BENZENE SULFONAMIDE:

Yield –41.45%, Melting point: 134-138^oC.

The IR spectrum of the synthesized product showed the aromatic OH at 3736 cm^{-1}, C=O at 1706 cm^{-1}, secondary N-H at 3336 cm^{-1}, S=O at 1366 cm^{-1} and primary N-H at 3498 cm^{-1}, aromatic amine C-N at 1322 cm^{-1}.

The Mass spectrum of the synthesized product shows the El MS m/z value of the compound is 379, consistent with the molecular formula of $C_{18}H_{16}N_2O_4S$ (356 +23Na) and the base peak for compound was found at 300.8.

The ^{1}H-NMR spectrum of the synthesized compound shows the signals of aromatic H singlet in the region δ= 7.3-7.5ppm is assigned to (4H), The singlet in the region of $NH_2\delta$=4.8ppm (2H), the aromatic OH group appears as doublet in the region of

δ= 6.9ppm (1H), The secondary NH appears as doublet in the region of δ=6.7ppm (1H).

In the ^{13}C-NMR the synthesized compound shows the signals in the range of =121.25ppm- 127.73ppm are attributed to the respective C1 to C7 in the naphthalene moiety and δ=197.05ppm is assigned for carbonyl carbon , δ =157.70 for aromatic hydroxyl carbon . δ=52.19ppm is assigned for methyl linkage carbon, δ=119.33ppm,128.37ppm -136.56ppm is assigned for the aniline carbons respectively.

CONCLUSION

Most of the naphthalene substituted compounds were found to possess diverse biological activities viz., antihypertensive, nasal decongestants, anti-inflammatory and antimicrobial agents. In the present research work, we have synthesized new sulfonamide derivative by introducing naphthalene moiety as a substituent to further evaluate for anti-microbial properties. We synthesized the novel compound and characterized by using IR, NMR and mass spectrometric techniques.

ACKNOWLEDGEMENT

The authors are thankful to management, principal and staff members of Chalapathi Institute of Pharmaceutical Sciences (Guntur) for their continuous support and encouragement to carry out this research work.

REFERENCES

[1] Y. B. Rokade and R. Z. Sayyed *et al*., published an article in Rasayan Journal of chemistry with title Naphthalene derivatives with a new range of antimicrobials with high therapeutic value, 2009, 972-980.

[2] Foye's principles of Medicinal Chemistry, sixth edition, published by Lippincott Williams & Wilkins, 773f, 1053, 1047t, 976f, 980t, 1121f, 1122.

[3] Website of Pediatric on Call Child health care, Targets and their Mechanism of action.

[4] Website of Drug bank, Target and their Mechanism of action.

[5] Noboru Hara, Takaki Mizusawa and Kota Takahashi, Published an Article in Division of Urology, with the title "The role of Naftopidil in the management of benign prostatic hyperplasia, 2011, 227-238.

[6] Manawwer Alam, Ateeq Rahman, Naser M. Alandis and Mohammed Rafi Shaik *et al*., published an article in Arabian journal of Chemistry with title "Ni/Silica catalyzed acetylation of phenols and naphthol.", 2012.

[7] Y. B. Rokade and R. Z. Sayyed *et al*., published an article in Rasayan

Journal of chemistry with title Naphthalene derivatives with a new range of antimicrobials with high therapeutic value, 2009, 972-980.

[8] Mei-Han Huang, Sheng-Nan Wu, Jih-Pyang Wang, Chen-Hsing Lin, Shih-l Lu, Li-Fang Liao and Ai-Yu Shen *et al*., published an article in Drug Development Research with title "Biological study of Naphthalene derivatives with Anti-Inflammatory activities.", 2003, vol 60.

[9] Vogel's, Textbook of Practical Organic Chemistry, 5th Edition, (1989) Pg. No: 1010.

[10] Jerry March, Textbook of Advanced Organic Chemistry, 4th Edition, (2007), Pg. No: 695-697. N-Bromosuccinimde reactions.

[11] Vogel's, Textbook of Practical Organic Chemistry, 5th Edition, (1989), Pg. No: 422. N-Bromosuccinimde reactions.

[12] V. K. Ahluwalia and Rakesh Kumar Parashar, Textbook of Organic Reaction Mechanisms, 3rd Edition, (2015), Pg. No: 203. Synthesis of N-Bromosuccinimde.

[13] Bodi Reddy Mohan Reddy *et al*., have published an article in chinese chemical letter with the title "Silica gel catalyzed alpha bromination of ketones using N-bromosuccinimde, 2014, 179-182.

[14] Kuo-Wei Huang *et al*., had published an article in Arabian journal of chemistry, which title "Effective and selective alpha bromination of carbonyl compounds using N-bromosuccinimde under microwave irradiation conditions", 2015, 892-896.

[15] Dasharath M. Chavhan *et al*., had published their research article in international journal of pharmacy and pharmaceutical research, with a title "Efficient ecofriendly and catalyst free synthesis of 1-[2-(4-substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide in PEG400 medium'', 2015, 168-176.

[16] Weicheng Zhou and Deyong Ye *et al*., had published their article in BEILSTEIN journal of organic chemistry with a title "A Novel and practical asymmetric synthesis of dapoxetine hydrochloride", 2015.

[17] Lauro Figueroa-Valverde *et al*., published an article in Asian Journal of Chemistry with the title of "Design and synthesis of Naphthol Derivative", vol: 25, No: 12, 2013, 6724-6726.

[18] Salam A. Ali *et al*., Published an article in International Journal of Current Microbiology and Applied Sciences, with title "Synthesis of some sulpha derivatives as antibacterial agents", vol: 5, No: 5, 2016, 75-83.

[19] Ramazan Erenler published an article with the title "Synthesis of Allenlic Naphthalene derivatives", Vol: 21, No: 2, 2007, 241-247.

[20] Instrumental method of chemical analysis by B.K.Sharma; twenty fourth revised and enlarged Edition 2005, 192-327.

[21] Fuyu Guan, Cornelius Uboh, Lawrence Soma, Anne Hess, Yi Luo, Deborah S. Tsang *et al*., published an article in Journal of Mass Spectroscopy, with title "sensitive liquid chromatographic/ tandem mass spectrometric method for determination of beclomethasone dipropionate and its metabolites in equine plasma and urine" in the year 2003, 823-838.

[22] Abdulkarim-Talaq Mohammad, Hasnah Osman and Guan-Yeow Yeap *et al*., published an article in International Journal of Spectroscopy, with the title "1,3-Oxazepane-4,7-Diones Compounds: ^{1}H and ^{13}C NMR High-Resolution Spectroscopy (1D and 2D)"in the year 2011, 4-5.