ejpmr, 2018, 5(4), 348-353

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SYNTHESIS AND BIOACTIVITY EVALUATION OF NEW BISSULFONAMIDES AND BISCARBAMATE DERIVATIVES OF 1,5-DIAMINONAPHTHALENE

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Article Received on 03/02/2018 **Article Revised on 24/02/2018** **Article Accepted on 16/03/2018**

ABSTRACT

Synthesis of a new series of N,N'-(Naphthalene-1,5-diyl)bis substituted sulfonamides 3(a-e) and N,N'-(Naphthalene-1,5-diyl)bis substituted carbamates 5(a-e) were synthesized from 1,5-diamino naphthalene **(1)** using various pharmacologically active sulfonyl chlorides **(2)** and choloformates **(4)** in the presence of mild base. The chemical structures were characterized by IR, ^{1}H and ^{13}C NMR, mass and elemental analysis. The biological assay revealed that the compounds **3d, 5b** exhibited high inhibition activity against anti bacterial and antifungal strains.

KEYWORDS: 1,5-diaminonaphthalene, sulfonamides, carbamates, antibacterial activity, antifungal activity.

INTRODUCTION

It is well known that antibiotics are revolutionized medicines in the 20th century because it was gained great development in controlling of infective diseases. It has been estimated that 16-21% of annual antibiotics used by human beings. Sulfonamide functional group containing sulfa drugs have revolutionalized biological activities in the field of medical sciences.[1] Folic acid an important chemical for the synthesis of bacterial DNA and RNA, is inhibited by sulfonamides. Due to such activity sulfonamides are also efficiently used in agricultural field for antibacterial activities.[2,3] Sulfonamide functional group containing drugs are also reported as potential anticancer,[4] anti HIV,[5] anti glaucoma,[6] anti obesity,[6] anti convulsant,[7] anti tumour,[8] anti viral,[9] anti platelet aggregation,[10] anti inflammatory,[11] anti malarial[12] and herbicidal[13] agents.

Organic carbamates have unique applications in pharmaceutical and medicinal chemistry, agrochemistry and polymer chemistry and additionally posses various biological properties, such as inhibition of HIV, anticancer, anticonvulsant, antiepileptic activity, enzyme inhibition,[14-19] anti diabetic, anti oxidant and anti malarial activity.[20-22] The carbamate derivatives of (2'-(1H-tetrazol-5-yl)-biphenyl-4-yi)methanamine, carvedilol, azaindole and morphalino aniline, which have been synthesized by our group, showed good antimicrobial and anti viral activity.[23-26]

Naphthalene is the most abundant component of coaltar. The liquid residue formed during the distillation of coal into coke. Naphthalene an important parent material to produce numerous substitution products used in the manufacture of dyes, insecticides, organic solvents and synthetic resins. Naphthalene is also used for moth repellents, fungicides, lubricants, explosives, wood preservatives, vermicides and Hydronaphthalenes. Several naphthalene containing drugs such as Nafacillin, Naftifine, Terbinafine, etc. which play a vital role in the control of microbial infections.[26]

In this study we report the synthesis and screening *in vitro* antimicrobial activities of sulfonamide and carbamate derivatives of 1,5-diaminonaphthalene.

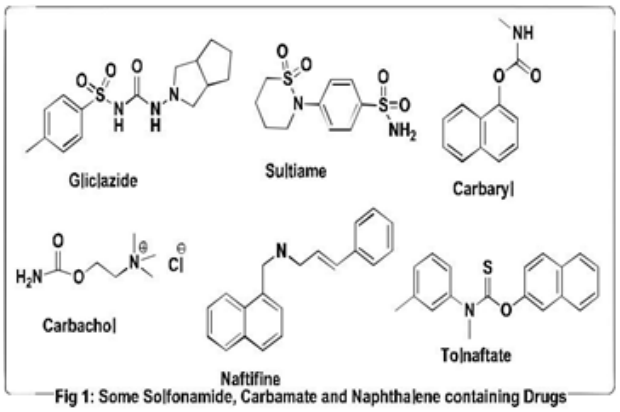


Fig 1: Some Solfonamide, Carbamate and Naphthalene containing Drugs

MATERIALS AND METHODS

1,5-diaminonaphthalene (1) and numerous substituted aryl sulfonyl chlorides and aliphatic /aryl chloroformates used in the study were purchased from Sigma-Aldrich

and used without further purification. The analytical grade solvents were procured from Merk. The process of the reaction was checked on Merk silica plates using 30-70% ethylacetate: hexane as mobile phase. Silica gel (160 mesh) was used in column chromatography for purification of the synthesized compounds. ^{1}H and ^{13}C NMR spectra were recorded on Bruker EXT spectrometer operating at 400.26 MHz for ^{1}H NMR and 125.0 MHz for ^{13}C NMR in dimethylsulfoxide (DMSO)-d_6/$CDCl_3$ solvent. Trimethylsilane (TMS) was used as the internal standard for the ^{1}H and ^{13}C NMR spectra. Chemical shifts were recorded on parts per million (ppm) and multiplicities are shown as Singlet (s), doublet (d), triplet (t), multiplet (m). Mass spectra were recorded on an MLP 2010 mass spectrometer. Elemental analysis was performed with a Thermo Finnigan Flash 1112 instrument. Melting points were recorded using Guna Digital melting point apparatus and are uncorrected, and they are expressed in degrees centigrade (˚C).

Synthesis of N,N'-(Naphthalene-1,5-diyl)bis 4-bromo benzene sulfonamide

1,5-diaminonaphthalene (**1)** (158 mg, 1 mmol) and triethylamine (TEA; 0.5 mL, 1mmol) in tetrahydrofuran (THF; 10 mL) was added the solution of 4-bromo benzenesulfonylchloride (2a; 510 mg, 2 mmol) in THF (3mL) slowly over 10 min at 10˚C. The reaction contents were heated to 50 C and then the reaction mixture was stirred vigorously for 3 hours. TLC was used to judge the completion of reaction using 30% ethylacetate: hexane as an eluent; the reaction mixture was cooled to room temperature and water was added. The solid was separated by filtration and recrystalized from a mixture of methanol and water (1:1) to give pure N,N'-(Naphthalene-1,5-diyl)bis 4-bromo benzene sulfonamide (**3a**). The same procedure was adopted to prepare the rest of sulfonamide derivatives 3(a-e) and carbamate derivatives 5(a-e) by reacting various substituted sulfonyl chlorides and chloroformates respectively. Some of the compounds were purified by column chromatography using ethyl acetate: hexane as a mobile phase.

Spectral Data of the Compounds

N,N'-(Naphthalene-1,5-diyl)bis 4-bromo benzene sulfonamide (3a)

Pale yash solid, yield: 89%, M.p; 233-235˚C; IR (KBR) ν_{max} (Cm^{-1}): 3324(N-H), 3063 (Ar-CH), 1363 (S=O); ^{1}H NMR (DMSO, 400 MHz): δ10.42 (s,1H, NH), 10.31(s, 1H, NH), 7.95(dd,2H, J= 8.4 MHz, Ar-H), 7.87(dd,2H, J=8.5 MHz, Ar-H), 7.80 (m,4H, Ar-H), 7.38 (m,4H, Ar-H); ^{13}C NMR (DMSO, 100 MHz): δ142.9(C-11), 141.5(C-12), 138.2(C-16,C-16'), 131.7(C-18, C-18'), 131.5(C-20, C-20'),129.3(C-17, C-17'), 129.1(C-21,C-21'), 126.2(C-19, C-19'), 126.0(C-8,C-3), 125.9(C-5,C-10), 111.5(C-4,C-9), 108.9(C-2,C-7). LC-MS (m/z); 595.89 $(M-H)^{+}$ (100%); Anal. Calcd for $C_{22}H_{16}N_2S_2Br_2O_4$: C,44.31; H,2.70;N,4.70. Found: C,44.29; H, 2.67; N, 4.68.

N,N'-(Naphthalene-1,5-diyl)bis 4-fluoro benzene sulfonamide (3b)

Pale white solid, yield: 86%, M.p; 243-245˚C; IR (KBR) ν_{max} (Cm^{-1}): 3327(N-H), 3104 (Ar-CH), 1368 (S=O); ^{1}H NMR (DMSO, 400 MHz):): δ10.30 (s,2H, NH), 7.95(d,2H, J= 4 MHz, Ar-H), 7.86(d,2H, J=8 MHz, Ar-H), 7.74 (m,4H, Ar-H), 7.45 (m,4H, Ar-H);), 7.20 (m,2H, Ar-H); ^{13}C NMR (DMSO, 100 MHz): δ167.0(C-19, C-19'), 142.1(C-11),141.9(C-12), 135.1(C-16,C-16'), 130.6(C-17,C-17'), 130.5(C-21,C-21'), 126.1(C-3,C-8), 125.1(C-5,C-10), 116.7(C-18,C-18'), 116.5(C-20,C-20'), 111.9(C-4,C-9), 110.3(C-2,C-7); LC-MS (m/z); 475.05 $(M-H)^{+}$ (100%); Anal. Calcd for $C_{22}H_{16}N_2S_2F_2O_4$: C,55.69; H,3.40;N,5.90. Found: C,54.49; H, 3.37; N,5.85.

N,N'-(Naphthalene-1,5-diyl)bis 4-chloro benzene sulfonamide(3c)

Pale white solid, yield: 90%, M.p; 242-244˚C; IR (KBR) ν_{max} (Cm^{-1}): 3337(N-H), 3076 (Ar-CH), 1148 (S=O); ^{1}H NMR (DMSO, 400 MHz): δ10.37 (s,2H, NH), 7.89(dd,2H, J=7. 2 MHz, Ar-H), 7.85(dd,2H, J=4 MHz, Ar-H), 7.73 (m,4H, Ar-H), 7.56 (m,4H, Ar-H);), 7.10 (d,2H, J=7.6 MHz,Ar-H); LC-MS (m/z); 507.02 $(M-H)^{+}$(100%):

N,N'-(Naphthalene-1,5-diyl)bis 2-nitro benzene sulfonamide (3d)

Pale yellow solid, yield: 88%, M.p; 223-225˚C; IR (KBR) ν_{max} (Cm^{-1}):): 3371(N-H), 3176 (Ar-CH), 1348 (S=O); ^{1}H NMR (DMSO, 400 MHz): δ10.29 (s,2H, NH), 8.29(dd,2H, J=7. 6 MHz, Ar-H), 8.15(dd,2H, J=4.2 MHz, Ar-H), 7.73 (m,2H, Ar-H), 7.46 (m,4H, Ar-H);), 7.10 (d,2H, J=7.4 MHz,Ar-H); LC-MS (m/z); 529.05 $(M-H)^{+}$ (100%):

N,N'-(Naphthalene-1,5-diyl)bis 4-chloro-3-nitro benzene sulfonamide (3e)

Pale white solid, yield: 85%, M.p; 243-245˚C; IR (KBR) ν_{max} (Cm^{-1}): 3332(N-H), 3204 (Ar-CH), 1385 (S=O); ^{1}H NMR (DMSO, 400 MHz):): δ9.42 (s,2H, NH), 8.48(dd,1H, J= 8 MHz, Ar-H), 8.33(dd,1H, J=8 MHz, Ar-H), 8.14 (m,4H, Ar-H), 7.62 (m,2H, Ar-H);), 7.46 (m,2H, Ar-H), 6.81 (dd,2H,J=7.6 MHz Ar-H); ^{13}C NMR (DMSO, 100 MHz): δ149.2, 149.0, 142.7,142.5, 139.3, 138.9,135.5,135.2,132.12,131.9,130.7,130.3,126.9,126.7, 125.6,125.2,125.0,124.9,112.1,111.9, 110.3, 110.0; LC-MS (m/z); 596.9 $(M-H)^{+}$ (100%); Anal. Calcd for $C_{22}H_{14}N_4S_2O_6Cl_2$: C,44.23; H,2.36;N,9.38. Found: C,43.47; H, 2.30; N,8.85.

Diisobutyl naphthalene-1,5-diyldicarbamate (5a)

Pale white solid, yield: 84%, M.p; 185-187˚C; IR (KBR) ν_{max} (Cm^{-1}): 3295(N-H), 3147 (Ar-CH), 2920(Ali Str),1753 (C=O); ^{1}H NMR (DMSO, 400 MHz):): δ9.52 (s,2H, NH), 7.9(d,2H, J= 8.4 MHz, Ar-H), 7.59(m,4H, Ar-H), 3.90 (d,4H,J=6.4 MHz, Ali-CH_2), 1.97 (m,2H, Ali-CH); 0.95 (d,6H,J=6MHz, -CH_3); ^{13}C NMR (DMSO, MHz): δ151.8(C-13,C-13'), 145.1(C-11),141.9(C-12), 126.1(C-3,C-8), 125.9(C-5,C-10), 118.7(C-C-4,C-9),

116.5, 105.3(C-2,C-7), 73.2(C-14,C-14'), 27.9(C-15,C-15'), 19.0(C-16,C-16'); LC-MS (m/z); 359.19 $(M-H)^+$ (100%); Anal. Calcd for $C_{20}H_{24}N_2O_4$: C,67.02; H,7.31;N,7.82. Found: C,64.49; H, 7.27; N,6.85.

Bis(2,2,2-trochloroethyl) naphthalene diyldicarbamate (5b)

White solid, yield: 86%, M.p; 190-192-˚C; IR (KBR) v_{max} (Cm^{-1}): 3361(N-H), 3149 (Ar-CH), 2975(Ali Str),1729 (C=O); ^{1}H NMR (DMSO, 400 MHz):): δ10.17 (s,2H, NH), 7.94(t,2H, J= 7.2 MHz, Ar-H), 7.71(m,4H, Ar-H), 4.97 (m,4H, $-CH_2$);^{13}C NMR (DMSO, 100 MHz): δ153.1(C13,C-13'), 140.9(C-11),140.7(C-12), 126.0(C-3,C-8), 125.9(C-5,C-10), 111.9(C-4,C-9), 104.8(C-2,C-7),96.5(C-16,C-16'), 69.8(C-15,C-15'); LC-MS (m/z); 507.09 $(M-H)^+$ (100%); Anal. Calcd for $C_{16}H_{12}N_2O_4Cl_6$: C,37.75; H,2.38;N,5.50. Found: C,35.94; H, 2.37; N,5.45.

Dimethyl naphthalene-1,5-diyldicarbamate (5c)

Pale yash solid, yield: 90%, M.p; 178-180˚C; IR (KBR) v_{max} (Cm^{-1}):): 3367(N-H), 3206 (Ar-CH),2917(Ali Str) 1733 (C=O); ^{1}H NMR (DMSO, 400 MHz): δ9.26 (s,2H, NH), 7.48(m,4H, Ar-H), 3.90(s,6H, $-CH_3$); LC-MS (m/z); 275.10 $(M-H)^+$ (100%):

Diethyl naphthalene-1,5-diyldicarbamate (5d)

Pale brown solid, yield: 85%, M.p; 170-175˚C; IR (KBR) v_{max} (Cm^{-1}):): 3363(N-H), 3145 (Ar-CH), 2957(Ali Str) 1731 (C=O); ^{1}H NMR (DMSO, 400 MHz): δ10.12 (s,2H, NH), 7.61(m,4H, Ar-H), 7.57(m,2H, Ar-H), 4.39 (m,4H, $-CH_2$), 1.20 (s,6H, $-CH_3$);); LC-MS (m/z); 303.13 $(M-H)^+$ (100%):

Dipentyl naphthalene-1,5-diyldicarbamate (5e)

Pale yash solid, yield: 86%, M.p; 123-125˚C; IR (KBR) v_{max} (Cm^{-1}):):3243(N-H), 3135 (Ar-CH), 2975(Ali Str),1727 (C=O); ^{1}H NMR (DMSO, 400 MHz): δ9.25 (s,2H, NH), 7.42(m,2H, Ar-H), 7.15(m,4H, Ar-H), 4.18 (s,4H, O-CH_2-CH_2), 1.44 (m,4H, -CH_2-CH_2);), 1.29 (s,4H, -CH_2) 0.94(s,6H,-CH_3); LC-MS (m/z); 387.20 $(M-H)^+$ (100%).

BIOLOGICAL EVALUATION

Antibacterial activity

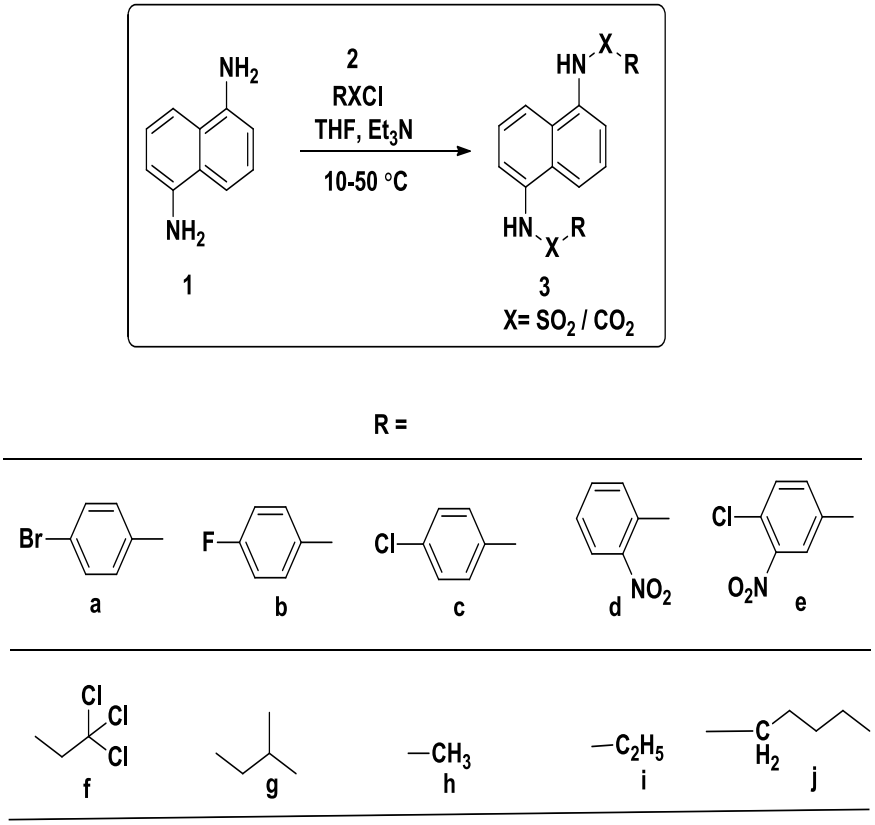
Test compounds were screened to determine their antibacterial activity against four bacterial strains; two Gram positive and two Gram negative bacteria by using disc diffusion method.[26-27] The organisms were cultured in nutrient broth at 37˚C for 24 hours. One percent broth culture containing approximately 10^6 colony-forming units (CFU/ml) of test strain was added to nutrient agar medium and poured in to sterile petri plates. The medium was allowed to solidify, five microliters of the test compound (40 mg/mL in DMSO) was poured on 6 mm sterile paper discs and placed on nutrient agar plates respectively. In each plate DMSO served as standard control and Pencillin served as an antibacterial standard drug. Triplicate plates of each bacterial strain were prepared. The plates were incubated at 37˚C for 24 hours. The antbacterial activity was determined by measuring the diameter of zones showing complete inhibition (mm).

RESULTS AND DISCUSSION

Chemistry

1,5-diaminonaphthalene was treated with various bio-potent sulfonyl chlorides 2(a-e) and chloroformates 4(a-e), in presence of triethylamine, to obtain the corresponding compound in good yields. The synthesis of various sulfonamide and carbamate derivatives is outlined in Scheme 1.

The structures of newly synthesized compounds 3(a-e) and 5(a-e) were characterized by IR, ^{1}H/^{13}C NMR, LCMS and Elemental analysis. IR spectra of the compounds displayed stong absorption bands at 1738-1721 (C=O sym str) and 1272-1230 (C-O str) cm^{-1} indicating the formation of carbamates. The absorption bands at 1368-1357, 1159-1145 and 997-959 cm^{-1} correspond to S=O asymmetric stretch, S=O symmetric stretch and S-N stretch, respectively. In ^{1}H NMR, for sulfonamides, peaks in the region δ8.48-6.75 ppm are assigned for aromatic protons, whereas for carbamates aliphatic proton signals are in the range of δ5.07-1.16 ppm respectively. In the ^{13}C NMR spectra of chloroformates for the carbonyl group (C=O), the peaks observed in the range of 140.6-137.3 ppm. Besides the NMR studies, mass spectra displayed the exact molecular ion peaks in positive mode. The physical data of the title compounds are summarized in Table 1.



Scheme 1: Synthesis of sulfonamides and carbamate derivatives of 1,5-diamionaphthalene.

Table 1: Physical Data of the synthesized compounds 3(a-j).

Compound	Time (h)	Yield (%)	m.p (˚C)
3a	3.5	89	233-235
3b	3.5	86	243-245
3c	4.0	90	242-244
3d	3.0	88	223-225
3e	3.5	85	243-245
5a	4.0	84	185-187
5b	4.5	86	190-192
5c	4.0	90	178-180
5d	3.5	85	170-173
5e	4.5	86	123-125

BIOLOGICAL ASSAY

Antibacterial activity

The antibacterial activity of newly synthesized compounds 3(a-e) and 5(a-e) were screened against two gram positive bacteria, *Bacillus subtilis, Staphylococcus aures* and two gram negative bacteria, *Escherichia coli, Klebsiella pneumoniae* using agar well diffusion method. Pencillin was used as a standard. All the synthesized compounds 3(a-j) were found to exhibit good to moderate antibacterial activity against tested strains. A few of the compounds showed significant activity, whereas **3c, 3b** and **5c** showed high activity and the results are presented in Table 2.

Bacterial culture and zone of inhibiton in mm				
Compound	**B. Subtilis**	**S. Aureus**	**E. Coli**	**K. Pneumoniae**
3a	10.7	10.5	10.8	10.5
3b	13.7	13.1	12.8	11.9
3c	14.3	14.0	15.7	12.6
3d	13.0	12.0	12.5	11.0
3e	10.3	10.0	10.5	10.4
5a	9.5	9.8	9.0	9.3
5b	10	9.5	9.4	9.7
5c	14.1	13.5	13.3	11.5
5d	9.2	9.2	9.8	9.6
5e	9.0	10.0	11.0	9.8
Pencillin	**16.7**	**17.2**	**16.4**	**18.2**

Conc -100 µg/mL

Antifungal activity

Antifungal activity of the title compounds was also screened against fungal pathogens such as *Aspergillus niger* and *Candida albicans* by a disc diffusion method using standard drug, Amphotericin. All the title compounds 3(a-j) exhibited good to moderate antifungal activity against tested fungal strains. A few of the compounds showed significant activity, whereas **3a, 3d** and **5b** showed high activity and the results are presented in Table 3.

Fungal culture and zone of inhibition in mm.		
Compound	**A. niger**	**C. albicans**
3a	10.5	9.7
3b	9.4	9.2
3c	9.0	9.1
3d	10.9	10.2
3e	10.0	9.7
5a	9.5	8.9
5b	10.3	9.8
5c	9.8	9.5
5d	8.2	8.4
5e	8.8	9.1
Amphotericin	**13.2**	**12.5**

CONCLUSION

In summery, a series of 1,5-diaminonaphthalene bissulfonamide and biscarbamate derivatives were synthesized and characterized by spectral data and evaluated their *in vitro* antimicrobial activity. The compounds **3a, 3c, 5b** and **5c** exhibited promising potential antimicrobial activity compared to other compounds.

ACKNOWLEDGEMENT

The author express grateful thanks to University Grants Commission, New Delhi for the award of Rajiv Gandhi National Fellowship-JRF for providing financial assistance.

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