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Synthesis and Biological Activity of N-Aryl-N'-Heteroaryl Carbamides

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Abstract

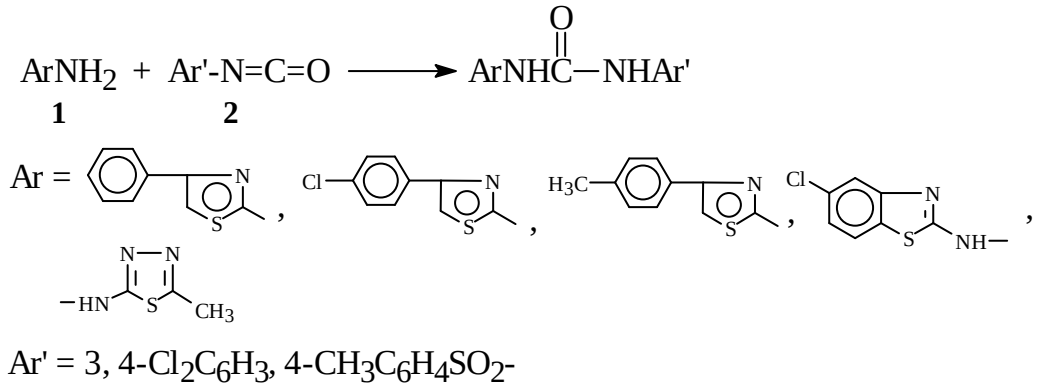
A series of N-aryl-N'-heteroaryl carbamides were synthesized. The structure of the compounds was established by means of I. R., [1]HNMR, Mass spectra and elemental analysis. All the compounds were screened for their antibacterial and antifungal activities. Compound 3e with chlorosubstitution was most active as antibacterial and antifungal with MIC of 0.075 mg/mL against E. coli and P. aruginosa.

Keywords: Carbamide, Thiazole, Thiadiazole, Antibacterial, Antifungal.

INTRODUCTION

Carbamide is a versatile pharmacophore present in many biologically active compounds. Various carbamides have shown anticonvulsant[1], hypoglycemic[2], anticancer[3], antiviral[4], antibacterial[5] and antifungal activities[6]. On the other hand 2-aminothiazole side chain has enhanced the antibacterial spectrum of cephalosporin[7]. It is present in third generation β-lactam antibiotics. In this context synthesis of thiazolyl ureas was undertaken with the aim that these two potential moieties will increase their biological profile.

The target compounds were prepared by the interaction of equimolar amounts of 2-amino-4-arylthiazole 2-aminobenzothiazole and 2-amino-1,3,4-thiadiazole with different aromatic isocyanates, according to Scheme-1. These N, N'-disubstituted carbamides were characterised by satisfactory elemental analysis, IR, [1]HNMR and Mass spectra.



Scheme 1 : Synthesis of carbamides

MATERIAL AND METHODS

All the chemicals were obtained from the Merck India (Pvt) Ltd., SD fine and Himedia. The chemicals and solvents used are of synthetic and AR grade respectively. Melting points were determined in open capillarty tubes on a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded for the compounds on Jasco PJ/IR 5300(KBr). The ^{1}HNMR spectra were recorded on JEOL-A2300 (Fourier Transform) instruments. Mass spectra were recorded on JEOL SX 102/DA-6000 Mass spectrometer. Elemental analysis (C, H, N, S) undertaken with Perkin Elmer Model 2400 analyser for all the compounds and were within ±0.4% of the calculated values. Aromatic isocyanates were prepared by literature methods.[8]

Preparation of 2-amino-4-phenylthiazole

2-Amino-4-phenylthiazole was prepared by heating a mixture of acetophenone (24.0 g; 0.2mol), thiourea (30.4g, 0.4mol) and iodine (50.8g, 0.2 mol) for 10 h on a steam bath. The crude reaction mixture was cooled and extracted with ether (40ml x 2) to remove the unreacted acetophenone and iodine. The residue was then dissolved in hot water and filtered to remove the sulfur and other impurities. The solution was then moderately cooled and basified with concentrated ammonia. 2-Amino-4-phenylthiazole thus precipitated was collected and recrystallised from ethanol water mixture, as colorless long shining needles. **Yield:** 375(63%); **m.p**. 150°C (lit. m.p. 152°C); **IR(KBr) cm^{-1}:** 3310, 3153(NH_2), 1624(C=N), 690(C-S-C); **^{1}HNMR(Acedone-d6) δppm:** 3.45(S, 2H, NH_2), 72.-8.1(m, 5H, ArH), 8.4(5,1H, thiazole).

Similarly, 2-amino-4-(4-chlorophenyl)thiazole-2-amino-4-(4-methyl phenyl)thiazole were prepared by using thiourea and 4-chloroacetophenone/4-methyl acetophenenone.

Preparation of 2-amino-6-chlorobenzothiazole[10]

A solution of liquid bromine (16.0g, 0.1 mol) in dry chloroform (30 ml) was slowly added with constant stirring into a suspension of 4-chlorophenylthiourea (18.65g, 0.1 mol) in dry chloroform (100 ml) during 30 minutes. The mixture was left for 3-4hr to complete the reaction. Chloroform was decanted and the product was suspended into water and sulfurdioxide gas was passed into it, till no more of the solid dissolved. It was filtered and the 2-amino-6-chlorobenzothiazole was precipitated by the addition of liquor ammonia. The precipitate was washed with water, dried and finally recrystallized from ethanol.

Yield: 15.4g(823%): **mp.** 196-97°C (Lit. mp. 198°C); **IR (KBr):** 3330, 3105 (NH_2), 1630 (C=N), 700(C-S-C) cm^{-1}; **NMR ($CDCl_3$) :** δ5.7(s, 2H, NH_2), 7.3-7.7(m, 4H, ArH).

Preparation of 2-amino-5-methyl-1,3,4-thiadiazole[11]:
A mixture of acetic acid (121 g, 2mol), sulfuric acid (100 ml, 99.9%, d=1.84, 2mol) and thiosemicarbazide (60g, 0.65mol) was boiled for 2h. Reaction mixture was then cooled and poured into ice water (400 ml). The 2-amino-5-methyl-1,3,4-thiadiazole was precipitated by neutralization with ammonium hydroxide solution (200 ml, 28%).
Yield: 70g (92%); **mp**. 222-223°C (Lit. mp. 223°); **IR(KBr) :** 3310, 3145 (NH_2), 1630(C=N), 690 (C-S-C) cm^{-1}; **NMR (Acetone d6) :** δ2.2 (s, 3H, CH_3), 4.5(s, 2H, NH_2).

N-(3,4-dichlorophenyl)-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-carbamide:
2-Amino-5-methyl-1,3,4-thiadiazole (5.75g, 0.05 mol) was mixed with 3,4-dichlorophenylisocyanate (9.4g, 0.05 mol) and the paste thus formed was warmed on a water bath for 2-3h. The excesas of isocyanate was washed with petroleum ether. The product was finally recrystallized from benzene.
Yield: 10g (66%); m.p. 233°C; **IR(KBr) :** 3447 (NH), 1680 (C=O), 1640 (C=N) cm^{-1}
NMR (DMSO-d6) : δ 2.3 (s, 3H, CH_3), 6.6(s, 1H, NH), 7.2-8.4(m, 3H, ArH); **Elemental Analysis:** Cald. for $C_{10}H_8Cl_2N_4OS$, C, 39.60; H, 2.64; N, 18.48; S, 10.56%. Found, C, 39.69; H, 2.80; N, 18.64; S, 10.69%.

Similarly, other compounds N-(3,4-dichlorophenyl)-N'-[4-(phenyl/4-chloropheny/4-tolyl)-thiazol-2-yl]-carbamide, N-(3,4-dichlorophenyl)-N'-[6-chlorobenzothiazol-2-yl]-carbamide were prepared, the details are given in Table-1.

Using 4-methylsulfonylisocyanate other compouds of the series were prepared and detailes of which are given in Table 1.

Spectral characteristics of N-aryl-N'-heteroaryl carbamides (3a-j)
N-(3,4-Dichlorophenyl)-N'-(4-phenyl-thiazol-2-yl) carbamide(3a):
IR(KBr, cm^{-1}): 3310(amide NH), 1645(NHCONH), 1620(C=C str in aromatic nuclei), 1510(amide II), 1470(C=N, thiazole) 850(strong, C-Cl), 690(C-S-C); **^{1}HNMR(DMSO-d6) δppm:** 6.57(s, 1H, D_2O exchangeable, aryl(NH), 7.2-7.5(m, 5H, phenyl H), 8.0-8.2(m, 3H, 3,4-diCl_2), 8.4(s, 1H, thiazole), 8.8(s, 1H, -CO-NH), Mass m/z: 328$[M]^+$, 330$[M+2]^+$, 332$[M+4]^+$

N-(3,4-Dichlorophenyl)-N-(4(4-chlorophenyl)-thiazol-2-yl carbamide (3b):
IR(KBr, cm^{-1}): 3315(amide NH), 1645(NHCOHN), 1625(C=C), 1510(amide II), 1475(C=N, thiazol), 855(strong, C-Cl), 692(-S-C); **^{1}HNMR(DMSO-d6) δppm:** 6.50(s, 1H, D_2O exchangeable, aryl NH), 7.2-7.4(m, 5H, phenyl H), 8.0-8.2(m, 3H, 3,4-diCl_2), 8.5(s, 1H, thiazole), 9.0(s, 1H, -CO-NH) Mass m/z: 327$[M]^+$, 329$[M+2]^+$, 331$[M+4]^+$, 333$[M+6]^+$

N-(3,4-Dichlorophenyl)-N'-(4(4-methylphenyl)-thiazol-2-yl) carbamide(3c)
IR(KBr, cm^{-1}): 3305(amide, NH), 1650(NH CONH), 1635(C=C), 1515(amide II), 1480(C=N, thiazole), 860(strong, C-Cl), 690(C-S-C); **^{1}HNMR(DMSO-d6) δppm:** 1.8(s, 3H, CH_3), 6.50(s, 1H, D_2O exchangeable, aryl(NH), 7.2-7.5(m, 4H, phenyl H), 8.1-8.3(m, 3H, 3,4-diCl_2); 8.6(s, 1H, thiazole), 9.1(s, 1H, -CO-NH), Mass m/z, 342$[M]^+$, 344$[M+2]^+$, 346$[M+4]^+$.

N-(3,4-Dichlorophenyl)-N'-(5-methyl-1,3,4-thiadiazol-2-yl) carbamide (3d):
IR(KBr, cm^{-1}): 3447(NH), 1680(NHCONH), 1640(C=N), 1635(C=C), 1515(amide II), 865(strong, C-Cl), 695(C-S-C); **^{1}HNMR(acetone-d6) δppm:** 2.2(s, 3H, CH_3), 6.6(s, 1H, aryl NH, D_2O exchangeable), 7.2-8.2(m, 3H, ArH), 8.9(s, 1H, -CONH), Mass m/z, 281$[M]^+$, 283$[M+2]^+$, 285$[M+4]^+$.

N-(3,4-Dichlorophenyl)-N'-(6-Chlorobenzothiazol-2-yl) carbamide (3e):
IR(KBr, cm^{-1}): 3460(-NH), 3030(C-H), 1660(-NHCONH-), 1642(C=N), 1580(Aromatic-H), 1515(amide II), 890-(strong, C-Cl); **^{1}HNMR(DMSO-d6) δppm:** 6.5(s, 1H, aryl NH, D_2O exchangeable), 7.5-7.8(m, 3H, benzothiazolyl), 8.5-8.6(m, 3H, 3,4-dichlorophneyl), 9.2(s, 1, -CONH) Mass m/z, 301$[M]^+$, 303$[M+2]^+$, 305$[M+4]^+$, 307$[M+6]^+$

N-(4-Methylphenylsulfonyl)-N'-[4-phenyl-thiazol-2-yl)-carbamide (3f).
IR(KBr cm^{-1}): 3465(-NH), 3035(C-H), 1665(-NHCONH-), 1640(C=N), 1575(aromatic C-H), 1510(amide II), 1350(SO_2), 1120(SO_2); **^{1}HNMR(DMSO-d6) δppm:** 2.1(s, 3H, Ar-CH_3), 6.15(s, 1H, aryl NH, D_2O exchangeable), 7.1-7.5(m, 5H, Ar-H), 7.9-8.0(m, 4H, Ar-SO_2), 8.5(s, 1H, thiazole), 9.1(s, 1H, -CONH) Mass m/z 373$[M]^+$

N-(4-Methylphenyl(sulfonyl)-N'-[4-(4-chlorophenyl)-thiazol-2-yl] carbamide (3g):
IR(KBr cm^{-1}): 3.460(-NH), 3032(C-H), 1666(-NHCONH-), 1645(C=N), 1580(Aromatic-H), 1518(amide II), 1352(SO_2), 1122(SO_2), 810(C-Cl); **^{1}HNMR(DMSO-d6) δppm:** 2.1(s, 3H, CH_3), 6.10(s,1H, Ar-NH), 7.1-7.5(m, 4H, -ArH), 7.8-6.0(m, 4H, C_6H_4, -SO_2), 8.8(s, 1H, CONH), 8.6(m, 1H, thiazole) Mass m/z 409$[M]^+$, 411$[M+2]^+$

N-(4-Methyl phenyl sulfonyl)-N'-[4-(4-methyl) phenyl)-thiazol-2-yl] carbamide (3h):
IR(KBr cm^{-1}): 3462(-NH), 3030(C-H), 1667(NHCONH), 1635(C=N), 1582(C-H Aromatic), 1520(amide II), 1352(SO_2), 1120(SO_2), 950-650(substituted aryl ring); **^{1}HNMR(DMSO-d6) δppm:** 2.1(s, 3H, Ph-CH_3), 2.5(s, 3H, Ph-SO_2), 6.2(s, 1H, ArylNH), 7.1-7.5(m, 4H, Aryl CH), 7.8-8.0(m, 4H, aryl(SO_2), 8.4(s, 1H, thiazole), 9.1(s, 1H, -CONH), Mass m/z 387$[M]^+$

N-(4-Methyl phenyl sulfonyl)-N'-5-methyl-1,3,4-thiadiazol-2-yl)-carbamide(3i)
IR(KBr cm^{-1}): 3447(NH), 3032(C-H), 1680(NHCONH), 1640(C=N), 1580(C-H, aromatic), 1525(amide II), 1350(SO_2), 1125(SO_2), 955(substituted aryl ring); **^{1}HNMR(DMSO-d6), δppm:** 2.5(s, 3H, thiadiazole), 2.8(s, 3H, phenyl sulfonyl), 6.2(s, 1H, NH, D_2O exchangeable), 7.8-8.2(m, 4H, aryl(SO_2), 9.2(s, 1H, -CONH) Mass, M/z 312$[M]^+$

N-(4-Methyl phenyl sulfonyl)-N'-(6-chlorobenzothiazol-2-yl)-carbamide (3j):
IR(KBr, cm^{-1}): 3445(NH), 3024(C-H), 1682(-NH-CO-NH-), 1530(amide II), 1353(SO_2), 1125(SO_2), 950-955(substituted phenyl), (C-Cl), 690(C-S-C); **^{1}HNMR(DMSO-d6), δppm:** 2.5(s, 3H, $ArSO_2(CH_3)$), 6.2(s, 1H, NH), 8.2-8.5(m, 4H, $PhSO_2$), 8.8(s, 1H, -CONH) Mass m/z, 435$[M]^+$, 437$[M+2]^+$.

Microbiological Testing
Antibacterial activity
The antibacterial activity was determined by agar dilution technique against 5 pathogenic bacteria, procured from the department of microbiology, IMS, BHU, Varanasi. The medium was prepared as per the instructions of the manufacturer of dry Mueller Hindon agar powder (Hi-Media). The concentrations of the test samples used were from 5000 μg/mL to lower concentration made by serial double dilutions with DMF. The minimum inhibitory, concentration (MIC) was taken as the lowest concentration (higher dilution) without visible growth. The study was simultanesously performed for the pure standard drugs (trimethoprim and sulfamethoxazole). The MICs are reported in Table 2.

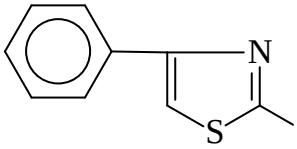
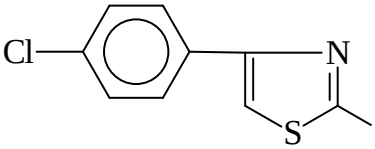
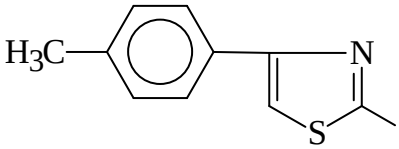
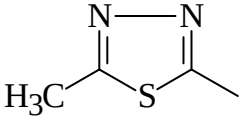
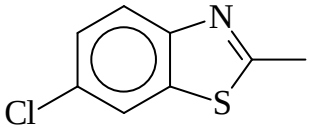
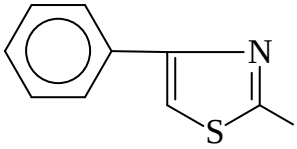
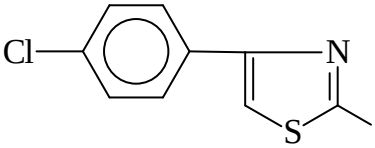
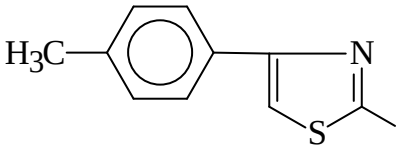
Antifungal activity:

The compounds were screened for antifungal sensitivity by agar dilution method at a concentration of 300 µg/mL against 3 pathogenic fungi. The compounds were starilized in DMF.

Table 1. Physical constant of N-Aryl-N'-heteroaryl carbamides (3a-j)

Ar-NHCoNHAr'

Ar' = 3,4-$Cl_2C_6H_3$

S. No.	Ar	Molecular formula	Yield (%)	m.p. (°C)	Elemental Analysis Calcd. (Found) % C	H	N	S
3a		$C_{16}H_{11}Cl_2N_3OS$	58	230	52.74 (52.39)	3.02 (3.24)	11.53 (11.73)	8.79 (8.59)
3b		$C_{16}H_{10}Cl_3N_3OS$	63	219	48.18 (48.13)	2.50 (2.30)	10.53 (10.53)	8.03 (8.39)
3c		$C_{17}H_{13}Cl_2N_3OS$	69	248	53.96 (54.01)	3.43 (3.40)	11.11 (11.19)	8.46 (8.39)
3d		$C_{10}H_8Cl_2N_4OS$	66	233	39.60 (39.69)	2.64 (2.80)	18.48 (18.64)	10.56 (10.69)
3e		$C_{14}H_8Cl_3N_3OS$	68	295	45.10 (44.99)	2.14 (2.04)	11.27 (11.21)	8.59 (8.57)
								Ar'= 4-$CH_3C_6H_4SO_2$
3f		$C_{17}H_{15}N_3O_3S_2$	61	190	54.69 (54.70)	4.02 (3.98)	11.26 (11.31)	17.15 (17.05)
3g		$C_{17}H_{14}ClN_3O_3S_2$	52	210	50.06 (49.93)	3.43 (3.39)	10.30 (10.27)	15.70 (15.63)
3h		$C_{18}H_{17}N_3O_3S_2$	47	170	55.81 (55.89)	4.39 (4.42)	10.85 (10.80)	16.53 (1645)

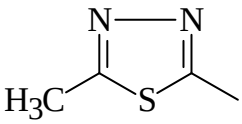
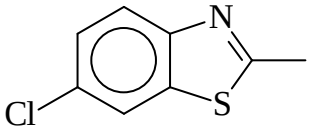
3i		$C_{11}H_{12}N_4O_3S_2$	56	233	42.30 (42.27)	3.84 (3.80)	17.94 (18.03)	20.51 (20.29)
3j		$C_{15}H_{12}ClN_3O_3S_2$	45	180	47.18 (47.08)	3.14 (3.20)	11.00 (10.97)	16.77 (16.83)

Table 2: Antibacterial and Antifungal Activities of N-aryl-N'-heteroaryl carbamides (3a-j)

Compd. No.	Antibacterial activity MIC µg/mL				Antifungal activity zone of inhibition (mm)	
	S. aureus	E. coli	P. aeruginosa	B. subtilis	C. albicans	A. niger
3a	39	78	78	156.25		
3b	4.88	2.44	0.3	39	20	28
3c	1250	25.00	2500	>5000	25	26
3d	1250	1250	>5000	625	24	23
3e	2.44	0.075	0.075	1.22	30	32
3f	19.5	9.76	78	2.44	24	21
3g	2.44	0.3	0.3	9.76	25	28
3h	78	156.25	312.5	39	20	22
3i	625	1250	625	1250	22	20
3j	0.075	9.76	1.22	2.44	30	28
Pyrimethamine	2500	2500	>5000	1250		
Sulfadoxine	156.25	150.25	1.22	0.15		
Fluconazole	-	-	-	-	30	28

RESULTS AND DISCUSSION

N-aryl-N'-heteroaryl carbamides were synthesised by reaction of appropriate heterocyclic amide with aroylisocyanates (Scheme 1). The compounds showed characteristic urea (-NH-CO-NH-) band in IR at 1680-1685 cm^{-1} besides other bands. In ^{1}HNMR spectra the methyl containing compounds gave 3H, singlet peak at 1.8-2.2 δppm (TMS standard). The mass spectra were in accordance with the molecular weight and specially chloro substituted compounds gave $[M+2]^+$ ion peaks.

All the compounds exhibited antibacterial activity against S. aureus, E. coli, P. aeruginosa and B. subtilis as compared to the standard drugs pyrimethamine and sulfoxadine. Compounds with chlorosubstitution in the aryl ring (3b, 3e, 3g and 3j were more active as compared to unsubstituted and methylsubstituted.

The antibacterial activity increased (lower MIC) as the number of chloro substituents increased in the molecule. The most active compounds 3e and 3f were active at MIC 0.075 mg/mL against E. coli, P. aeruginosa and S. aureus respectively. The lead molecule identified in these studeis was N-(3,4-dichlorophenyl)-N-(6-chlorobenzothiazol-2-yl) carbamide (3e).
In the antifungal test all the compounds inhibited the fungal growth of (albicans and A. niger. In this test also chloro compounds were most active.

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