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SYNTHESIS OF 2-[(5-ARYL-1,3,4-OXADIAZOL-2-YL)THIO]-*N*-(2-PHENYL-1,8-NAPHTHYRIDIN-3-YL)ACETAMIDE AND 2-[SUBSTITUTED-(1*H*-BENZO[*d*]IMIDAZOL-2-YL)THIO]-*N*-(2-PHENYL-1,8-NAPHTHYRIDIN-3-YL)ACETAMIDE DERIVATIVES ASANTIBACTERIAL AGENTS

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ABSTRACT

Several derivatives of 2-[(5-aryl-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamides and also 2-[substituted-(1*H*-benzo[*d*]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide derivatives were synthesized starting from the common intermediate 2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide and its reaction with 5-aryl-1,3,4-oxadiazole-2-thione or appropriate 1*H*-benzo[*d*]imidazole-2-thiols, respectively. All newly synthesized compounds were elucidated by IR, NMR, Mass spectra and elemental analysis. The titled compounds were examined for their antibacterial activity and found to be with significant activity.

Keywords: 1,8-naphthyridine, Benzimidazole, 1,3,4-oxadiazole, *N*-chloroacetamide, antibacterial activity

INTRODUCTION

The 1,8-naphthyridine, benzimidazole and 1,3,4-oxadiazole scaffolds (**Fig.1**) are some of the basic skeletons occur in the broad range of bioactive molecules. These heterocyclic motifs are useful in a variety of pharmaceutical and chemical fields. In particular, the 1,8-naphthyridine and its derivatives have gained great importance in biological activities such as antibacterial[1], anticonvulsant[2], anti-HIV[3], antioxidant[4], antihypertensive[5], anti-inflammatory[6]and antitumor[7]. Similarly, benzimidazole and 1,3,4-oxadiazoles exhibited a fascinating array of biological significances like antimicrobial[8,9], analgesic[10,11], anticancer[12,13] and anti-tubercular activities.[14,15]

In the past decade, a number of drugs bearing amide moiety were found to possess antimicrobial activity. For example, penicillins and cephalosporins are known for the effective treatment of various infectious diseases. These antibacterials have cyclic amide and acetamide moieties under the class of β-lactam. Recently, medicinal chemists have identified the Teixobactin (cyclic undecapeptide) and its analogs that possess a new hope for antibiotic activity, which acts against only Gram-positive bacteria such as MRSA[16]. The growing of resistance power to antimicrobial agents has indicated to the failure for the medicine of some bacterial and fungal infections. Therefore, there is a rapid emergence for the development of novel effective antibiotics with good selectivity in opposition to the infections and an advance for the medical future.

Researchers have tried to develop a combination of various heterocyclic motifs into a single molecular scaffold for highly efficacious. In recent years, an amalgamation of various benzimidazole or 1,3,4-

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oxadiazole motifs on merging with acetamides into one core structure *via* a sulfur linkage has reported with a view of biological aspects.[17-19]

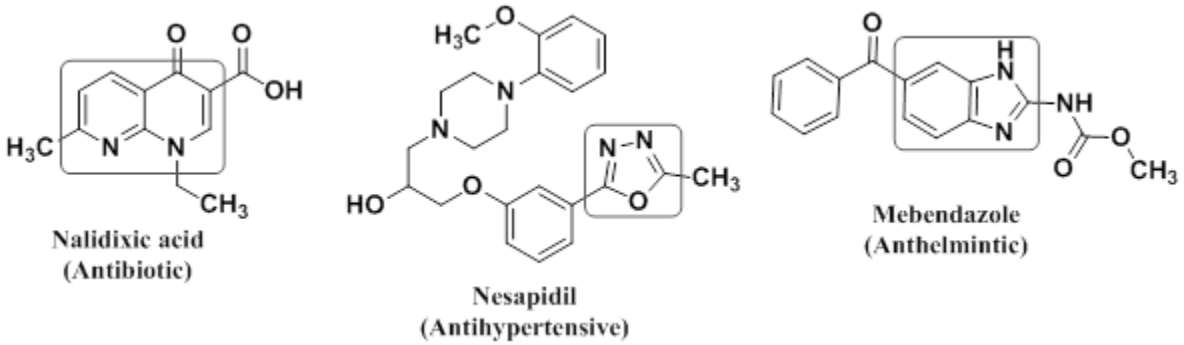


Fig.-1: Representative Bioactive Drugs like Naphthyridine, 1,3,4-oxadiazole and Benzimidazole Analogs

Inspired by these observations, and continuation of our attention in the synthesis of 1,8-naphthyridines[20], we, here in the report a new class of benzimidazole and also oxadiazole linked 1,8-naphthyridines *via* sulfur linkage and to study the additive effect of these scaffolds towards the antibacterial action.

EXPERIMENTAL

General Information

All reagents were used as purchased from commercial sources. The IR spectra were measured by employing the KBr pellets on a Shimadzu FT-IR spectrometer and stated in cm^{-1}. NMR spectra were obtained on Bruker spectrometer operating at 400 and 300 MHz for ^1H NMR, and 100 MHz for ^{13}C NMR, utilizing solvent is DMSO-d_6 or $CDCl_3$. The chemical shifts are reported in δ-ppm scale and the downfield from TMS. The *J*-values are given Hertz (Hz). Elemental analyses were reported by using an Elementar Vario Micro Cube analyzer. MS determinations were conducted by the ESI method on waters Alliance mass spectroscopic instrument. All melting points are uncorrected. The reactions and purity were checked by pre-coated TLC plates (silica gel 60F254, Merck) and spots visualized under UV irradiation.

Synthesis of 2-chloro-*N*-(2-phenyl-1,8-naphthyridine-3-yl)acetamide (2)

A solution of 2-phenyl-1,8-naphthyridine-3-amine (**1**) (5 mmol) and triethylamine (7.5 mmol) in dry DMF (30 mL) was cooled to 0°C. To this solution, chloroacetyl chloride (7.5 mmol) was added portion-wise and the mixture was stirred at R.T. for 5 hours (monitored by TLC). After that, the content was slowly poured on to stirred ice-cold water (50 mL) and the product was taken up inEtOAc (2x50 mL). The organic extracts were successively washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), filtered and evaporated. Purification by column chromatography (SiO_2, ethyl acetate/hexane, 2:8) afforded the required compound (**2**).

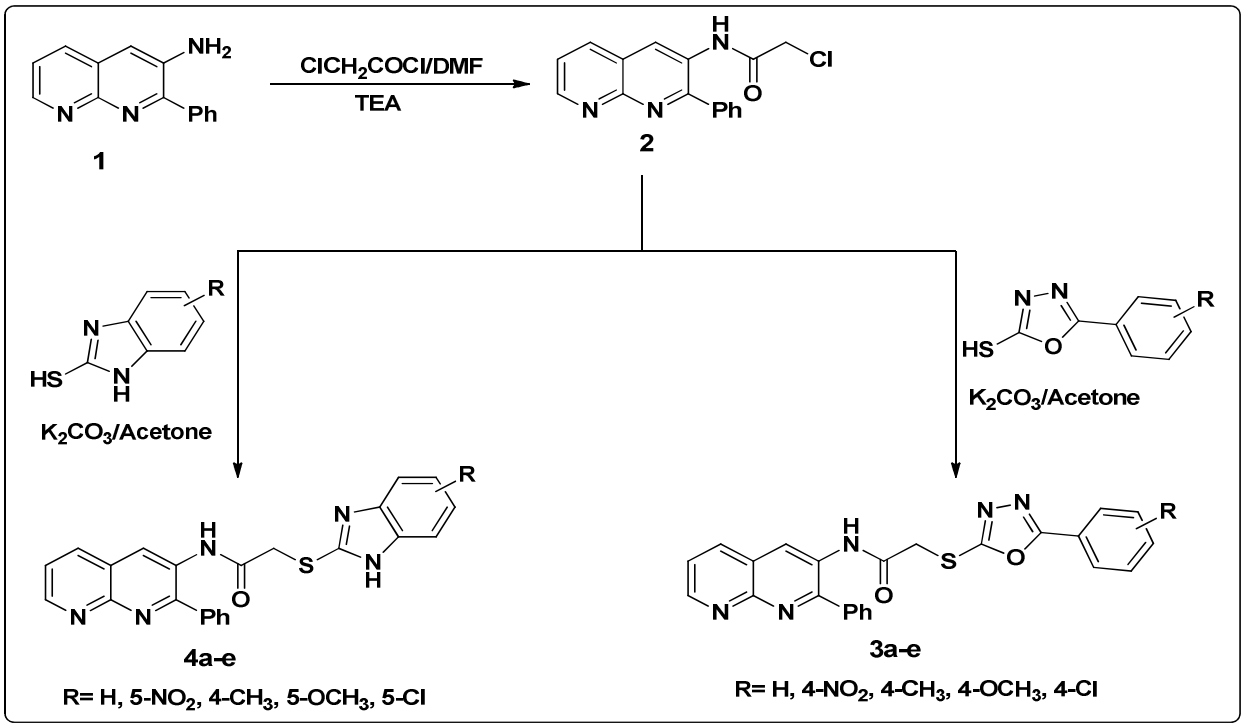
Synthesis of 2-[(5-substituted-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridine-3-yl)acetamide (3a-e)

Compound **2** (2 mmol), anhydrous K_2CO_3 (2 mmol) were taken in dry acetone (20 mL) and added to this a solution of an appropriate 1,3,4-oxadiazole-2-thiols (2 mmol) in dry acetone(10 mL). The obtained mixture was stirred at R.T. for 8 hours (monitored by TLC) and it was filtered. The filtrate was concentrated under vacuum and ice-cold water (20 mL) is added and stirred for 20 minutes. The formed precipitate was filtered, dried and purification by column chromatography (SiO_2, ethyl acetate/hexane,5:95) to acquire the title compounds (**3a-e**).

Synthesis of 2-[substituted-(1*H*-benzo[*d*]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridine-3-yl)acetamide (4a-e)

To a mixture of compound **2** (2 mmol), substituted benzimidazole-2-thiols (2 mmol) and anhydrous K_2CO_3 (2mmol) in dry acetone (30 mL) were stirred at R.T. for 8 hours (monitored by TLC). After this

time, the solvent was removed under vacuum and the residue stirred for 20 minutes in ice-cold water. The precipitate was filtered, dried and purification by column chromatography (SiO_2, hexane/EtOAc, 95:5) to get the titlecompounds (**4a-e**).



Scheme-1: Synthetic Protocol of the Compounds 3a-e and 4a-e

Spectroscopic and Analytical Data

2-chloro-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (2)

Off-white solid, m.p.: 284ºC, yield: 82%, IR (KBr): 3205 (N-H), 1666 (carbonyl), 1523, 1467; ^{1}H NMR (DMSO-d_6): 4.30 (2H, s, CH_2), 7.67 (6H, m), 8.54 (1H, dd, *J*=8.1, 1.5); 8.72 (1H, s), 9.07 (1H, d, *J*= 2.3); 10.13 (1H, S, NH); ^{13}C NMR (DMSO-d_6): 42.83 (CH_2), 121.69, 122.68, 128.37, 129.03, 129.20, 129.34, 132.95, 137.12, 137.49, 153.06, 153.51, 157.27, 165.46 (carbonyl). MS: $[M+1]^+$=298; Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.11; O, 5.37. Found: C, 64.59; H, 4.09; Cl, 11.93; N, 14.15; O, 5.41.

2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (3a)

Light yellow solid. IR (KBr): 3359 (amide N-H), 1687 (carbonyl), 1069 (C-O-C, oxadiazole), 729 (C-S).^{1}H NMR ($CDCl_3$+DMSO-d_6): 4.04 (2H, s,-S-CH_2), 7.36 (2H, d, *J*=2.35), 7.53 (6H, m), 7.85 (1H, s, -NH), 7.99 (4H, d, *J*=6.5), 8.22 (1H, d, *J*=7.47), 9.04 (1H, d, *J*=2.4).^{13}C NMR ($CDCl_3$+DMSO-d_6):34.38 (-S-CH_2), 125.28, 126.41, 126.94, 127.19, 128.89, 129.34, 130.27, 131.53, 132.33, 133.19, 133.57, 133.85, 134.10, 134.43, 134.74, 135.20, 141.19, 141.62, 151.45, 153.38, 157.21, 168.66 (carbonyl), 169.48 (oxadiazole, C-2).MS (*m/z*): 440 $[M+1]^+$. Anal. Calcd.for $C_{24}H_{17}N_5O_2S$: C, 65.59; H, 3.90; N, 15.94; O, 7.28; S, 7.30. Found:C, 65.64; H, 3.93; N, 15.99; O, 7.29; S, 7.33.

2-[(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (3b)

Pale yellow solid. IR (KBr): 3340 (amide N-H), 1687 (carbonyl), 1085 (C-O-C, oxadiazole), 727 (C-S).^{1}H NMR ($CDCl_3$): 3.29 (2H, s, -S-CH_2), 7.48 (5H, m), 7.69 (2H, d, *J*=6.23), 7.81 (1H, d, *J* =7.85), 8.09 (2H, dd, *J*=8.11, 1.72), 8.36 (1H, d, *J*=8.86), 8.78 (1H, s, -NH), 9.01 (1H, dd, *J*=4.16, 1.76), 9.07 (1H, s).^{13}C NMR ($CDCl_3$): 34.30 (-S-CH_2), 126.31, 127.28, 127.52, 128.26, 130.93, 131.64, 132.04, 132.35, 132.60, 133.42, 133.66, 133.83, 134.18, 134.30, 134.42, 134.87, 141.19, 141.62, 152.28, 153.40,

157.47, 168.66(C=O), 172.78 (oxadiazole, C-2).MS (*m/z*):485 $[M+1]^+$.Anal. Calcd.for$C_{24}H_{16}N_6O_4S$: C, 59.50; H, 3.33; N, 17.35; O, 13.21; S, 6.62. Found:C, 59.55; H, 3.34; N, 17.38; O, 13.23; S, 6.66.

2-[(1*H*-benzo[*d*]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (4a)
White solid. IR (KBr): 3143 (amide N-H), 3235 (NH, benzimidazole), 1691 (carbonyl), 739 (C-S).^{1}H NMR ($CDCl_3$+DMSO-d_6): 4.04 (2H, s, -S-CH_2), 6.99 (6H, m), 7.25 (1H, *J*=7.72) 7.46 (1H, dd, *J*=8.08, 4.02), 7.65 (2H, d, *J*=7.32), 8.21 (1H, d, *J*=6.65), 8.95 (2H, d, *J*=8.34), 10.77 (1H, s, NH, amide), 12.15 (1H, s, NH, benzimidazole).^{13}C NMR (DMSO-d_6): 35.31 (CH_2), 113.46, 121.35, 121.66, 122.04, 127.66, 128.51, 128.60, 129.14, 129.89, 136.54, 149.41, 152.25, 155.86, 167.90 (carbonyl).MS (*m/z*): 412 $[M+1]^{+1}$. Anal. Calcd.for $C_{23}H_{17}N_5OS$: C, 67.13; H, 4.16; N, 17.02; O, 3.89; S, 7.79. Found: C, 67.16; H, 4.19; N, 17.05; O, 3.90; S, 7.82.

2-[(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)thio]-*N*-(2-phenyl-1,8-naphthyridin-3-yl)acetamide (4e)
Light yellow solid. IR (KBr): 3189 (amide N-H), 3289 (NH, benzimidazole), 1692 (carbonyl), 1539, 732 (C-S).^{1}H NMR ($CDCl_3$+DMSO-d_6): 4.04 (2H, s, -S-CH_2), 7.02 (5H, m), 7.28 (1H, *J*=7.63) 7.45 (1H, dd, *J*=8.05, 4.04), 7.70 (2H, d, *J*=7.28), 8.19 (1H, d, *J*=6.59), 8.94 (2H, d, *J*=8.27), 10.77 (1H, s, NH, amide), 12.15 (1H, s, NH, benzimidazole).^{13}C NMR (DMSO-d_6): 35.31 (CH_2), 115.33, 121.48, 121.94, 123.15, 127.81, 128.34, 128.58, 129.19, 129.74, 133.08, 135.27, 149.48, 153.43, 155.77, 168.13 (carbonyl).MS (*m/z*): 446 $[M+1]^{+1}$. Anal. Calcd. for $C_{23}H_{16}ClN_5OS$: C, 61.95; H, 3.62; Cl, 7.95; N, 15.71; O, 3.59; S, 7.19. Found: C, 61.98; H, 3.63; Cl, 7.98; N, 15.75; O, 3.62; S, 7.21.

Table-1: Optimized Reaction Conditions for Compound 2

Entry	Solvent	Base	Time (h)	Temp. (0^0C)	Yields (%)[a]
1	DMF	K_2CO_3	8	RT	32
2	$CHCl_3$	K_2CO_3	4	Reflux	25
3	AcOH	NaOAc	5	RT	48
4	DMF	TEA	5	RT	79
5	DMF	DIPEA	5	RT	54

[a] isolated yields

RESULTS AND DISCUSSION

The synthetic route for the hybrid compounds of 1,8-naphthyridine based benzimidazoles(**3a-e**) and/or oxadiazoles(**4a-e**)were outlined in Scheme-1. The required intermediate 2-chloro-*N*-(2-phenyl-1,8-naphthyridine-3-yl)acetamide (**2**) was afforded by chloroacetylation reaction between the 2-phenyl-1,8-naphthyridine-3-amine (**1**) andchloroacetyl chloride under basic conditions. Interestingly, we found that DMF would enhance the rate of reaction while the TEA could promote the amide product (**2**) and these optimized conditions were listed in the Table-1. Further, this moiety (**2**) was treated with various oxadiazole-2-thiols or benzimidazole-2-thiols in presence of potassium carbonate as a scavenger under mild conditions to give final compounds (**3a-e and 4a-e**). In this step, the base favors the thiol form, which is susceptible to nucleophilic substitution reaction. The structures of all the synthesized compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS spectral and elemental data analysis. The physical data of synthesized compounds were illustrated in Table-2.

In IR spectra, compounds **2**, **3a-e** and **4a-e**were showed the significant stretching frequencies of amide carbonyl groups at the region of 1692-1666 cm^{-1}. The –NH band of amide function was observed at the region of 3359-3205 cm^{-1} andthe -CH_2-S-band of the final compounds was witnessed in the area of 740-727 cm^{-1}.

In ^{1}H NMR spectra of compounds (**2, 3a-e and 4a-e**), the amide -NH proton appeared at the zone of 7.85-10.77 ppm and the -NH proton of benzimidazole nucleus (**4a-e**) was founded at the region of 12.15-12.22 ppm in the form of singlets. The characteristic methylene (CH_2) protons were apparent at 3.29-4.30 ppm region as a singlet. These methylene protons provide an evidence for the generation of –CH_2–S– linkage in titled compounds. Conversely, this singlet unambiguously shifted from 4.30 ppm in compound **2** to

3.29-3.85 ppm in compounds **3a-e** and **4a-e** in final compounds. In ^{13}C NMR spectra, the carbonyl function of the synthesized compounds resonated at 165.46-168.85 ppm and methylene (CH_2) carbon appeared at 34.30-42.83 ppm. The remaining signals were observed at their expected region. In mass spectra, all the compounds furnished the corresponding molecular ion peaks, which were matched with the calculated molecular weight, respectively.

Table-2: Physical Data of the Newly Synthesized Compounds 3a-e and 4a-e

Entry	Compound	R =	Melting points(°C)	Yield[a] (%)
1	3a	H	170-172	82
2	3b	4-NO_2	178-180	79
3	3c	4-CH_3	235-236	77
4	3d	4-OCH_3	182-184	81
5	3e	4-Cl	216-218	82
6	4a	H	225-226	80
7	4b	5-NO_2	196-198	77
8	4c	4-CH_3	242-244	75
9	4d	5-OCH_3	204-206	78
10	4e	5-Cl	258-260	81

[a]Isolated yields after purification

Antibacterial Activity

To determine the *in vitro* antibacterial activity of the final analogs**3a-e** and **4a-e**were screened against the selected Gram-positive bacteria strain like *S.aureus* and *E.Faecalis* and the selected Gram-negative bacteria strain like *E.coli* and *P.aeruginosa*. This activity was resolved to make the use of disk diffusion method at 20 µg/mL and 40 µg/mL concentrations in DMSO as a solvent. The investigation results were compared with ciprofloxacin utilized as a standard drug and zone of inhibition was expressed in terms of mm**.**

In all the screening compounds, **3b, 3d and 4d** were exhibited outstanding antibacterial activity against microorganisms. However, the remaining screened compounds were demonstrated moderate to weak activity than the reference drug. So, the final compounds with a different substituent on rings and the minimum inhibition zone diameter results can be seen in Table-3.

Table-3: Biological Activity of Final Compounds against the Microorganisms

Compound	Minimum Inhibition Zone Diameter(mm) at Various Concentrations							
	Gram (+ve)Bacteria				Gram (-ve)Bacteria			
	S.aureus (conc. in µg/mL)		*E.Faecalis* (conc. in µg/mL)		*E.coli* (conc. in µg/mL)		*P.aeruginosa* (conc. in µg/mL)	
	20	40	20	40	20	40	20	40
3a	10	20	08	16	07	14	08	16
3b	17	30	18	33	18	34	26	38
3c	12	24	10	16	09	16	11	18
3d	16	29	16	29	17	32	24	35
3e	08	18	10	18	08	09	08	14
4a	13	23	10	21	07	15	25	19
4b	10	27	12	23	18	28	09	14
4c	08	16	11	21	12	20	14	19
4d	16	32	18	34	23	35	28	37
4e	12	20	08	14	07	16	20	28
Ciprofloxacin (Std.)	15	28	16	30	18	35	23	35

CONCLUSION

In conclusion, we have successfully synthesized a series of hybrid compounds such as benzimidazole and oxadiazole bearing 1,8-naphthyridine derivatives in good yield. All the synthesized compounds were characterized by IR, NMR, Mass spectra and elemental analyses. Most of the titled 1,8-naphthyridine derivatives displayed remarkable antibacterial activity. Among the evaluated compounds **3b**, **3d** and **4d** were exhibiting a maximal zone of inhibition against the bacterial strains.

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