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Synthesis of some New Imidazolones and 1,2,4-Triazoles Bearing Benzo[b]thiophene Nucleus as Antimicrobial Agents

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Abstract

2-Phenyl-1-(3′,5′-dichloro-2′-benzo(b)thiophenoylamino)-4-arylidine-5-imidazolones **(2a-j)** were prepared from the 2-hydrazinocarbonyl-3,5-dichlorobenzo[b]thiophene **1** by the reaction with different oxazolinone which were prepared by the condensation of substituted benzaldehyde with benzoyl glycine in presence of sodium acetate and acetic anhydride. Reaction of **1** with different aromatic isothiocyanate afforded the corresponding N^1-(3′,5′-dichlorobenzo[b]thiophen-2′-yl)-N^4-substituted aryl thiosemicarbazides **(3a-j)**. Compounds **(3a-j)** on reaction with sodium hydroxide yielded 3-(3′,5′-dichlorobenzo[b]thiophen-2′-yl)-4-aryl-5-mercapto-1,2,4-triazoles **(4a-j)**. The pharmacological evaluations were performed for their antitubercular and antimicrobial activities. Some novel imidazolones and 1,2,4-triazoles were synthesized and evaluated for *in vitro* antibacterial activity against *Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 6380, *Bacillus megaterium* ATCC 14581, *Staphylococcus aureus* ATCC 29213, and antifungal activity against *Aspergillus niger* ATCC 9029. The *in vitro* antimycobacterial activity of the new compounds was also investigated against *Mycobacterium tuberculosis* $H_{37}RV$ (ATCC 27294) in BACTEC 12B medium using the ALAMAR radiometric system. The structures of new compounds were supported by IR, ^{1}H-NMR and Mass spectral data.

Keywords: Imidazolones; 1,2,4-Triazoles; Benzo[b]thiophene; Antimicrobial activity; Antitubercular activity

Introduction

Imidazolones and their derivatives are known for their potential biological and pharmacological properties [1]. Synthesis of imidazolones from the respective oxazoline-5(4H)-ones and appropriate primary amines under different experimental conditions has been investigated by Islam *et al.* [2-3].

Derivatives of 1,2,4-triazoles are of current interest in view of their wide ranging of biological activities exhibited by these compounds [4-7]. Search of more biologically effective agent and industrial utility, led

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chemists to explore a variety of chemical entities with biological properties. In continuous of our work on benzo[b]thiophene nucleus [8], it was contemplated to synthesized some new 1,2,4-triazoles and imidazolones derivatives bearing benzo[b]thiophene moiety.

Condensation of 2-hydrazinocarbonyl-3,5-dichlorobenzo[b]thiophene **1** with different aromatic oxazolinones led to the required compounds 2-phenyl-1-(3′,5′-dichloro-2′-benzo[b]thiophenoylamino)-4-arylidine-5-imidazolone **(2a-l)**. Reaction of **1** with different aromatic isothiocyanates yielded N^1-(3′,5′-dichloro-2′-benzo[b]thiophenyl)-N^4-substituted aryl thiosemicarbazides **(3a-j)**, which on reaction with sodium hydroxide yielded 3-(3′,5′-dichlorobenzo[b]thiophen-2′-yl)-4-aryl-5-mercapto-1,2,4-triazoles**(4a-j)**.

The structures of the synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}HNMR and Mass spectral data. The compounds were screened for their antitubercular and antimicrobial activities.

Experimental

Melting points were taken in open capillary tubes and are presented uncorrected. IR spectra (KBr) (cm^{-1}) were recorded on Shimadzu-8400 FTIR spectrophotometer and ^{1}H NMR spectra were recorded on Brucker spectrometer (300 MHz) using TMS as an internal standard (chemical shift in δ ppm). The purity of the compounds was checked on silica gel plates. All the synthesized compounds gave satisfactory elemental analysis.

Synthesis of 4-Arylidine-2-phenyl-5-oxazolinones

These compounds were prepared by the condensation of substituted benzaldehyde with benzoyl glycine in the presence of sodium acetate and Vogel described acetic anhydride as.

Synthesis of 2-Phenyl-1-(3',5'-dichloro-2'-benzo[b]thiophenoylamino)-4-arylidine-5-imidazolones (2a-l)

A mixture of 2-hydrazinocarbonyl-3,5-dichlorobenzo[b]thiophene (2.61 g, 0.01 M) and 4-arylidine-2-phenyl-5-oxazolinone (0.01 M) in pyridine (20 ml) was refluxed for 6-8 h. The excess of solvent was removed under reduce pressure and reaction mixture was poured onto crushed ice. The product was isolated and crystallized from benzene. **2h** Yield 64%, m.p. 130-132°C. Anal. Calcd. for $C_{26}H_{17}N_3O_3SCl_2$, Calcd. C, 59.77; H, 3.25; N, 8.04%. Found C, 59.72; H, 3.23; N, 8.01%. IR (KBr υ_{max} cm^{-1}): 1787 (C=O), 1598 (C=N), 781 (C-Cl), 696 (C-S-C). ^{1}H NMR (300 MHz) (δ ppm): 6.90-7.60 (m, 12H, Ar-H + -CH), 8.19 (s, 1H, -NH), 3.87 (s, 3H, $-OCH_3$) MS = m/z (522 M^+).

Similarly, other imidazolones have been prepared. The physical constants are recorded in Table 1.

Synthesis of N^1-(3',5'-dichloro-2'-benzo[b]thiophenyl)-N^4-substituted-aryl thiosemicarbazides (3a-j)

A mixture of 2-hydrazinocarbonyl-3,5-dichlorobenzo(b)thiophene (2.61 g, 0.01 M) and 4-arylisothiocynate (0.01 M) was refluxed in ethanol for 6 h. The resulting solution was then cooled and separated solid was crystallized from ethanol. **3f**: Yield 64%, m.p. 65-67°C. Anal. Calcd. for $C_{17}H_{13}N_3O_2S_2Cl_2$, Calcd. C, 47.88; H, 3.05; N, 9.86%. Found C, 47.80; H, 3.02; N, 9.84%. IR (KBr υ_{max} cm^{-1}): 3197 (N-H, sec. amine), 1672 (C=O, sec. amide), 1199 (C=S), 781 (C-Cl), 680 (C-S-C). ^{1}H NMR (300 MHz)(δ ppm): 3.96 (s, 3H, $-OCH_3$), 6.94 (d, 2H, Ar-H), 7.37(d, 2H, Ar-H), 7.05-7.80 (m, 3H, Ar-H), 8.21 (s, 1H, O=C-NH) and 8.58 (s, 1H, S=C-NH). MS= m/z (427 M^+).

Similarly, other thiosemicarbazides have been prepared. The physical constants are recorded in Table 1.

Synthesis of 3-(3',5'-Dichloro-2'-benzo[b]thiophenyl)-4-aryl-5-mercapto-1,2,4-triazoles (4a-j)

N^1-(3′,5′-dichlorobenzo[b]thiophen-2′-yl)-N^4-substituted aryl thiosemicarba-zide (0.01 M) was refluxed with sodium hydroxide solution (8%, 20 ml) for 8 h. The content was cooled, poured into cold water, stirred and filtered. The filtrate on neutralizing yielded solid, which was crystallized from ethanol. **4f**: Yield, 69%, m.p. 260-261°C. Anal. Calcd. for $C_{17}H_{11}N_3OS_2Cl_2$, Calcd. C, 50.00; H, 2.70; N, 10.29%. Found C, 49.56; H, 2.68; N, 10.28%. IR (KBr υ_{max} cm^{-1}): 1630 (C=N, triazole), 746 (C-Cl), 680 (C-S-C). ^{1}H NMR (300 MHz) (δ ppm): 3.91 (s, 3H, $-OCH_3$), 6.90-7.78 (m, 7H, Ar-H).

Similarly, other 1,2,4-triazoles have been prepared. The physical constants are recorded in Table 1. NMR spectra data of compounds **2a-j** and **4a-j** are summarized in Table 4.

Result and Discussion

Antimicrobial Activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method [9] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against

Table 1. Physical data of compounds **2a-l**, **3a-j** and **4a-j**

Compounds	R	Molecular formula	m.p. (°C)	Yield (%)
2a	C_6H_5	$C_{25}H_{15}N_3O_2SCl_2$	120-121	66
2b	3-Br, C_6H_4	$C_{25}H_{14}N_3O_2SCl_2Br$	90-100	62
2c	3-Cl, C_6H_4	$C_{25}H_{14}N_3O_2SCl_3$	130-131	65
2d	2-CI,5-CH_3,C_9H_4N	$C_{29}H_{17}N_4O_2SCl_3$	130-131	61
2e	2-OH, C_6H_4	$C_{25}H_{15}N_3O_3SCl_2$	118-119	61
2f	4-OH-C_6H_4	$C_{25}H_{15}N_3O_3SCl_2$	80-81	63
2g	3-OCH_3,4-OH, C_6H_3	$C_{26}H_{17}N_3O_4SCl_2$	100-101	67
2h	4-OCH_3, C_6H_4	$C_{26}H_{17}N_3O_3SCl_2$	130-131	64
2i	4-$N(CH_3)_2$, C_6H_4	$C_{27}H_{20}N_4O_2SCl_2$	140-141	62
2j	2-NO_2, C_6H_4	$C_{25}H_{14}N_4O_4SCl_2$	98-99	65
2k	3-C_6H_5-O, C_6H_4	$C_{31}H_{19}N_3O_3SCl_2$	158-159	60
2l	4-SCH_3, C_6H_4	$C_{26}H_{17}N_3O_2S_2Cl_2$	145-146	60
3a	C_6H_5	$C_{16}H_{11}N_3OS_2Cl_2$	155-156	60
3b	2-Cl, C_6H_4	$C_{16}H_{10}N_3OS_2Cl_3$	105-106	58
3c	3-Cl, C_6H_4	$C_{16}H_{10}N_3OS_2Cl_3$	130-131	61
3d	2-CI, 5-CH_3, C_6H_3	$C_{17}H_{12}N_3OS_2Cl_3$	110-111	65
3e	2,3-$(CH_3)_2$, C_6H_3	$C_{18}H_{15}N_3OS_2Cl_2$	160-161	68
3f	2-OCH_3, C_6H_4	$C_{17}H_{13}N_3O_2S_2Cl_2$	65-66	64
3g	2-CH_3, C_6H_4	$C_{17}H_{13}N_3OS_2Cl_2$	120-121	59
3h	4-CH_3, C_6H_4	$C_{17}H_{13}N_3OS_2Cl_2$	150-151	50
3i	2-NO_2, C_6H_4	$C_{16}H_{10}N_4O_3S_2Cl_2$	80-81	62
3j	4-NO_2, C_6H_4	$C_{16}H_{10}N_4O_3S_2Cl_2$	100-101	64
4a	C_6H_5	$C_{16}H_9N_3S_2Cl_2$	190-191	68
4b	2-Cl, C_6H_4	$C_{16}H_8N_3S_2Cl_3$	270-271	67
4c	2-CI, 5-CH_3, C_6H_3	$C_{17}H_{10}N_3S_2Cl_3$	228-229	68
4d	3-Cl, C_6H_4	$C_{16}H_8N_3S_2Cl_3$	270-271	64
4e	2,3-$(CH_3)_2$, C_6H_3	$C_{18}H_{13}N_3S_2Cl_2$	280-281	70
4f	2-OCH_3, C_6H_4	$C_{17}H_{11}N_3OS_2Cl_2$	260-261	69
4g	2-CH_3, C_6H_4	$C_{17}H_{11}N_3S_2Cl_2$	265-266	66
4h	4-CH_3, C_6H_4	$C_{17}H_{11}N_3S_2Cl_2$	253-254	68
4i	2-NO_2, C_6H_4	$C_{16}H_8N_4O_2S_2Cl_2$	280-281	71
4j	4-NO_2, C_6H_4	$C_{16}H_8N_4O_2S_2Cl_2$	280-281	70

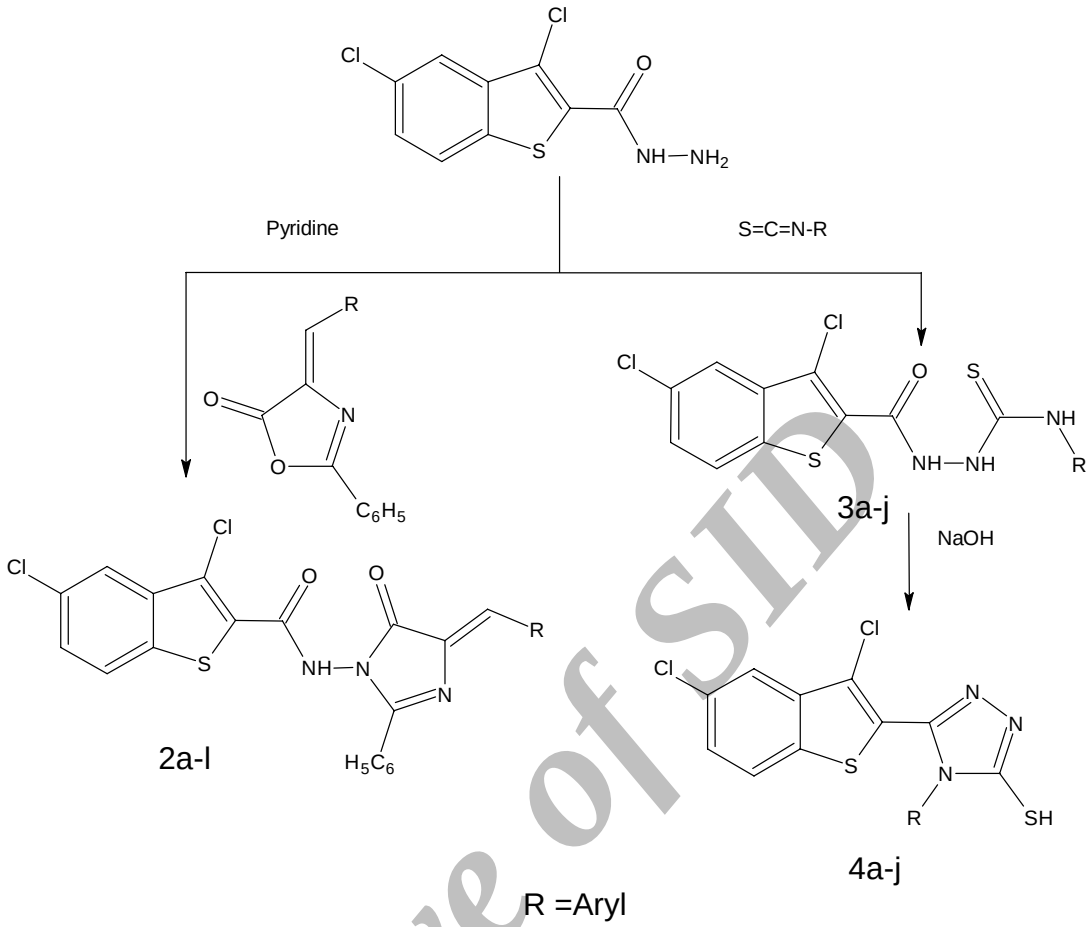
varieties of bacterial strains such as *Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 6380, *Bacillus megaterium* ATCC 14581, *Staphylococcus aureus* ATCC 29213, and antifungal activity against *Aspergillus niger* ATCC 9029 at 40 µg/ml concentrations. Standard drugs like Ampicillin, Amoxycillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for the comparison purpose (Table 2). Compounds **2d**, **2g**, **4g** and **4j** were active against *E. coli.* **2d**, **2g**, **4g** and **4j** were active against *P. vulgaris,* **2b**, **2c**, **2j**, **4h** and **4i** were active against *B. mega.* **2f**, **2k**, **2l**, **4h**, **4i** and **4j** against *S. aureus.* **2h**, **2i**, **4d** and **4i** displayed maximum activity against *A. niger*.

Antitubercular Activity

The antitubercular evaluation was carried out at Tuberculosis and Antimicrobial Acquisition Co-ordinating Facility (TAACF) USA. Antitubercular activity was evaluated at 6.25 µg/ml concentration

Table 2. Antimicrobial screening results of compounds **2a-l**, **3a-j** and **4a-j**

Compounds	Antibacterial activity zones of inhibition in mm				Antifungal activity
	E. coli	*P. aeruginosa*	*B. mega*	*S. aureus*	*A. niger*
2a	15	14	15	18	18
2b	15	18	15	12	19
2c	15	18	15	19	16
2d	20	22	15	19	14
2e	14	11	12	20	18
2f	14	11	12	30	20
2g	20	19	14	19	15
2h	14	14	13	20	22
2i	14	14	12	20	26
2j	15	14	15	20	20
2k	12	11	10	30	20
2l	14	15	10	30	14
3a	14	10	15	20	15
3b	20	11	16	19	19
3c	15	18	16	16	11
3d	14	10	14	19	20
3e	12	15	13	30	20
3f	12	15	14	25	10
3g	15	14	15	19	20
3h	16	14	22	18	10
3i	18	18	11	22	20
3j	16	15	18	19	12
4a	16	14	10	10	18
4b	18	16	14	14	19
4c	20	16	12	12	20
4d	17	17	10	10	20
4e	18	18	15	15	20
4f	15	11	15	15	17
4g	22	25	10	10	12
4h	12	11	22	22	17
4i	12	11	22	22	25
4j	22	23	15	25	10
Benzyl penicillin	20	30	20	26	0
Amoxycillin	17	25	10	20	0
Ciprofloxacin	26	15	15	28	0
Erythromycin	22	30	15	30	0
Griseofulvin	0	0	0	0	22



Reaction Scheme

Table 3. Antitubercular screening result of compounds which shows high percentage of inhibition

Compounds	MIC (µg/ml)	% Inhibition
2b	>6.25	67
2e	>6.25	31
2h	>6.25	40
2j	>6.25	71
3e	>6.25	28
4g	>6.25	25
4h	>6.25	64

against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the ALAMAR radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 µg/ml concentration which showed 98% inhibition. The data of compounds are recorded in Table 3.

The antitubercular activity of Imidazolones and 1,2,4-triazoles were found in the range of 64% to 71% growth of inhibition, while the 3-bromo, 2-nitro group of imidazolone and 4-methyl group of 1,2,4-triazole nucleus display maximum activity.

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Table 4. NMR spectral data of compounds **2a-l** and **4a-j**

Compounds	R	NMR Value in δppm	
		X	Ar-H
2a	C_6H_5	-	7.02-8.50(m,15H)
2b	3-Br, C_6H_4	-	6.89-8.20(m,14H)
2c	3-Cl, C_6H_4	-	6.95-8.50(m,14H)
2d	2-CI,5-CH_3,C_9H_4N	2.49(s,3H,-CH_3)	6.91-8.15(m,14H)
2e	2-OH, C_6H_4	-	6.88-7.98(m,15H)
2f	4-OH-C_6H_4	-	6.92-8.23(m,15H)
2g	3-OCH_3,4-OH, C_6H_3	3.83(s,3H,OCH_3)	6.93-8.28(m,14H)
2h	4-OCH_3, C_6H_4	3.87(s,3H,-OCH_3)	6.90-7.60(m,14H)
2i	4-$N(CH_3)_2$, C_6H_4	2.42(s,6H,-CH_3)	6.83-8.25(m,14H)
2j	2-NO_2, C_6H_4	-	6.75-8.03(m,14H)
2k	3-C_6H_5-O, C_6H_4	-	6.45-8.54(m,19H)
2l	4-SCH_3, C_6H_4	2.52(s,3H,-SCH_3)	6.93-8.11(m,14H)
4a	C_6H_5	-	6.85-8.12(m,9H)
4b	2-Cl, C_6H_4	-	6.81-8.10(m,8H)
4c	2-CI, 5-CH_3, C_6H_3	2.39(s,3H,-CH_3)	6.82-7.95(m,7H)
4d	3-Cl, C_6H_4		6.82-7.99(m,8H)
4e	2,3-$(CH_3)_2$, C_6H_3	2.40(s,6H,-CH_3)	6.80-8.15(m,7H)
4f	2-OCH_3, C_6H_4	3.91(s,3H,OCH_3)	6.90-7.78(m,8H)
4g	2-CH_3, C_6H_4	2.45(s,3H,CH_3)	6.97-8.11(m,8H)
4h	4-CH_3, C_6H_4	2.75(s,3H,-CH_3)	6.99-8.15(m,8H)
4i	2-NO_2, C_6H_4	-	6.93-8.15(m,8H)
4j	4-NO_2, C_6H_4	-	6.91-8.09(m,8H)

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