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Research Article

Synthesis of New 1,5-Benzothiazepines and Isoxazolines Bearing Quinolino and Sulphonamido Pharmacophores

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Abstract: A series of new 2-(2-Chloro-substitutedquinilino-3'-yl)-3-(4'-toulylsulphonyl aminophenyl)-2,3-dihydro-1,5-benzothiazepines (**4**) and 3-(4'-tosylaminophenyl)-5-(2'-chloro-substituted quinolin-3-yl)-4,5-dihydroisoxazolines (**5**) have been prepared by separately carrying cyclocondensation of new 3-(2-chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino)phenyl) prop-2-en-1-ones (**3**) with 2-aminothiophenol and hydroxylamine hydrochloride, respectively. The intermediates 2-propen-1-ones (**3**) were obtained by condensing 2-chloro-substitutedquinoline-3-carbaldehydes with 4-methyl sulphonamido acetophenone. The synthesized compounds have been screened for their antibacterial activity.

Introduction

1,5-Benzothiazepine derivatives are particular interest for lead discovery because they have been found active against different families of targets [1]. The 1,5-benzothiazepine scaffold has also displayed activities like anti-inflammatory [2], anticancer [3], vasodilating [4], cardiopritective [5] and anti-HIV [6]. The compounds bearing this structural unit possess a broad spectrum of biological activities such as antianginal [7], squalene synthetase inhibitor [8], V_2 arginine vasopressin receptor antagonist [9] and HIV-1 reverse transcriptase inhibitor [10]. Dandia *et al*. synthesize a series of 1,5-benzothiazepines and studied their cytotoxicity [11].

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Isoxazolines are found to display a wide range of biological activities [12]. Substituted isoxazolines have revealed anti-influenza virus [13], antifungal [14], antitubercular [15], spermicidal and anti-HIV [16] properties. Isoxazolines are gaining importance as potential building block for wide variety of complex molecules [17].Recently Ahmed Kamal *et al.* reported 3,5-diaryl isoxazoline/isoxazole linked 2,3-dihydroquinazo linone hybrids as anticancer agents [18,19].

Quinoline ring system also play vital role in nature due to their industrial importance and wide range of biological activities including antitumor [20], anti-inflammatory, analgesic [21] and antihistamine [22]. Quinolines have been used to synthesize various fused

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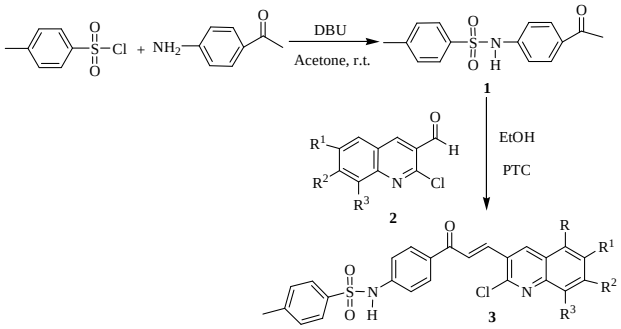
heterocyclic ring systems which also show a wide range of pharmacological activities [23-26].
Sulfonamides are an important class of biologically active compounds. Indeed, the sulfonamides continue to play important role in chemotherapy alone or in the combination of other drugs [27]. Recently attention is paid on the synthesis of sulfonamides possessing heteryl moieties [28] and sulphamethizole, sulfamoxazole and sulfafenazole are explored as clinical agents.

Literature survey reveals that when one biodynamic heterocyclic system is coupled the generated molecule displays enhanced biological activity [29]. The chemistry of these linked bi-heterocycles has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile [30]. In view of these observations, great importance of these heteryl nuclei and in continuation our work on the synthesis of heterocycles linked with sulfonamides [31], here it was thought worthwhile to synthesize novel chalcones, 1,5-benzothiazepines and isoxazolines in order to explore the biological activity of these compounds.

In the present work an attempt has been made to synthesize new 3-(2-chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino) phenyl)prop-2-en-1-ones, 2-(2-Chloro-substituted quinilino-3'-yl)-3-(4'toulylsulphonyl aminophenyl)-2,3-dihydro-1,5-benzothiazepines and 3-(4'-tosylaminophenyl)-5-(2'-chloro-substitutedquinolin-3-yl)-4,5-dihydroisoxazolines having sulphonamido and quinoline moieties/pharmacophores.

Results and Discussion

The key intermediates, 3-formyl-2-chloro substitutedquinolines (**2**) were synthesized using the Vilsmeier-Haack reagent according to literature procedure [32]. 4-Methyl sulphonamido acetophenone (**1**) required for the synthesis was obtained by allowing the condensation of 4-amino acetophenone with p-toluenesulphonyl chloride using DBU (1,8-diazabicyclo [5,4,0]undec-7-ene) in acetone at room temperature. The compounds (**3**), chalcones were prepared by condensing 2-chloro-substituted quinoline-3-carbaldhydes (**2**) and 4-methyl sulphonamido acetophenone (**1**) in alcoholic KOH. The cyclocondensation of compound (**3**) with 2-aminothiophenol has been carried in ethanol (**4**) in presence of bi-catalyst and obtained 1,5-benzothiazepines (**4**) with good yield. The titled isoxazolines were synthesized by cyclocondensing 2-propene-1-ones (**3**) with hydroxylamine hydrochloride in alkaline medium. The reaction sequence is outlined in **Scheme 1** and **2**.



Scheme 1

The new compounds and intermediates have been characterized by IR, ^{1}H NMR and mass analyses. The spectral details for representative compounds are given in the experimental section.

Antibacterial Activity

Most of the synthesized compounds were screened *in vitro* for their antibacterial activities against three strains of bacteria (Staphylococcus aureus, Bacillus subtillis and Escherichia coli). Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at

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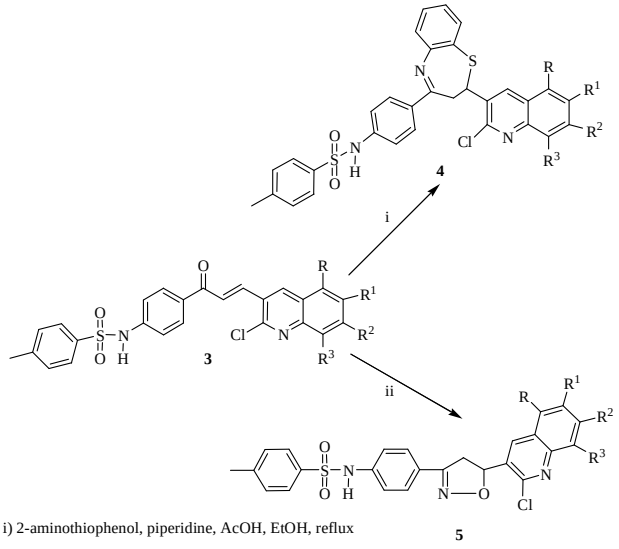
37 ^{o}C for 18 h. The agar plates of media were prepared and wells were made in the plate.

Each plate was inoculated with 18 h old cultures (100 µl, 10^{-4} cfu) and spread evenly on the plate. After 20 min, the wells were filled with of compound at different concentrations. The control wells with Streptomycin and Penicillin were also prepared. All the plates were incubated at 37 ^{o}C for 24 h and the diameter of inhibition zone were noted. Data of the compounds 4a-d and 5a-d are presented in **Table 4a-c** as the minimal inhibitory concentration (MIC µg).



i) 2-aminothiophenol, piperidine, AcOH, EtOH, reflux

ii) $NH_2OH.HCl$, KOH, E tOH, reflux

Scheme 2

Table 1. Physical data of chalcones, 2-propene-1-ones (**3a-e**).

Products	R	R^1	R^2	R^3	Yield (%)	Mp (^{o}C)
3a	H	H	H	H	68	178-180
3b	H	H	CH_3	H	65	261-263
3c	H	OCH_2CH_3	H	H	60	244-246
3d	H	Cl	H	H	62	135-137
3e	H	H	H	CH_3	66	250-252

Table 2. Physical data of 1,5-benzothiazepines (4a-e).

Products	R	R^1	R^2	R^3	Yield (%)	Mp (^{o}C)
4a	H	H	H	H	75	113-115
4b	H	H	CH_3	H	66	80-82
4c	H	OCH_2CH_3	H	H	68	120-121
4d	H	Cl	H	H	62	77-79
4e	H	H	H	CH_3	70	74-76

Table 3. Physical data of isoxazolines (5a-e).

Products	R	R^1	R^2	R^3	Yield (%)	Mp (^{o}C)
5a	H	H	H	H	72	134-136
5b	H	H	CH_3	H	62	197-199
5c	H	OCH_2CH_3	H	H	70	131-133
5d	H	Cl	H	H	60	137-139
5e	H	H	H	CH_3	66	156-158

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Table 4a *Antibacterial activity against B substillis.*

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
4a	0.8	0.9	1.3	1.4	1.5	1.8	< 0.0625
4b	1.1	1.2	1.4	1.7	1.8	2.2	< 0.0625
4c	0	0	0.8	0.9	1.5	1.9	0.25
4d	0.6	0.8	0.8	1	1.1	1.2	< 0.0625
5a	0	0	0	0	0.5	0.7	1
5b	0	0	0.7	0.8	1.2	1.6	0.25
5c	0	0	0	0	0	0.9	2
5d	0	0	0	0	0	0.8	2
	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
Streptomycin	1.2	1.4	2.1	2.4	2.6	2.8	< 25
Penicillin	0	0	0.8	1.5	2	2.5	100

Table 4b *Antibacterial activity against S aureus.*

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
4a	0.6	0.7	0.8	2.1	2.5	2.7	< 0.0625
4b	1.2	1.3	1.4	1.5	1.6	2	< 0.0625
4c	0.8	1	1.1	1.3	1.5	1.6	< 0.0625
4d	1.5	1.3	1.5	1.7	1.8	2	< 0.0625
5a	0	0.5	0.6	0.7	0.8	1.4	0.125
5b	0	1.4	1.5	1.6	1.8	1.8	0.125
5c	0	1	1.2	1.3	1.4	1.9	0.125
5d	0	1	1.2	1.3	1.2	1.6	0.125
	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
Streptomycin	0.7	1.5	2	2.4	2.5	2.7	< 25
Penicillin	0	1.1	1.5	1.6	2.1	2.3	50

Table 4c *Antibacterial activity against E.coli.*

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
4a	0.4	0.5	1	1.1	1.2	1.3	0.0625
4b	1.5	1.7	2	2.1	2.3	4	< 0.0625
4c	0	0	0.5	1	1.3	1.7	0.25
4d	1.6	1.7	1.8	1.9	2.1	2.2	< 0.0625
5a	0	0	0	0	0	0.7	2
5b	0	0	0	0	0	0.8	2
5c	0	0	0	0.5	1.1	1.3	0.5
5d	0	0	0	0	0	0.5	2
	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
Streptomycin	1.7	1.8	1.1	1.2	2.6	2.7	< 25
Penicillin	0	0.3	0.8	1.5	1.6	2.2	50

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Experimental section

General Remarks:

All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries and are uncorrected. The IR Spectra were recorded on a FT-IR (JASCO FT-IR) Japan. The ^{1}HNMR was measured on Bruker DRX-300, 300 MH_Z FT-NMR with low and high temperature in DMSO using TMS as internal reference. Mass spectra were recorded on an Ieo SX 102/DA-600 mass spectrometer.

Synthesis of 4-methyl sulphonamido acetophenone (1a).

p-Toluenesulphonyl chloride (0.002 mole), 4-amino acetophenone (0.002 mole) and DBU (0.001 mole) were dissolved in dry acetone (15 mL). The reaction solution was stirred at room temperature. The reaction was monitored by TLC. After 6 h of the reaction, the content of the flask was then poured on crushed ice. The obtained solid was filtered, washed with water, dried and crystallized from ethanol.

Yield 85%, mp 206-208 ^oC, IR (KBr) cm^{-1} 3270, 1670, 1340 and 1159. ^{1}HNMR (DMSO-d_6) δ: 2.31 (s, 3H, CH_3), 2.44 (s, 3H, $COCH_3$), 7 17 to 7.82 (m, 8H, J = 8 Hz Ar-H) and 10.77 (s, 1H, NH exchange with D_2O). MS (scanning mode ES^+): m/z 290 (M^+).

Synthesis of 3-(2-chloro-quinolin-3-yl)-1-(4-(tosylamino) phenyl)prop-2-en-1-ones (3a).

A mixture of 4-methyl sulphonamido acetophenone (0.01 mole) and potassium hydroxide (0.029 mole) was dissolved in ethanol (25 mL). To this solution 2-chloroquinoline-3-carbaldehyde (0.01 mole) was added in portion at 0-5 ^oC with constant stirring. In this reaction mixture catalytical amount of phase transfer catalyst (tetraethyl ammonium bromide) was added and then reaction mixture was further stirred for 3 h. by keeping the reaction temperature below 10 ^oC. It was then allowed to stand at room temperature for overnight. The reaction progress was monitored by TLC. After completion of the reaction it was poured on crushed ice and neutralized by acetic acid, the solid appeared was filtered, washed with cold water and crystallised from ethanol.

Yield 70%, mp 178-180 ^oC, IR (KBr) cm^{-1}: 3181, 1650, 1602, 1336 and 1161, 1286. ^{1}HNMR (DMSO-d_6) δ: 2.32 (S, 3H, CH_3), 7.18 to 8.02 (m, 12H, Ar-H), 7.48 (d 1H, CH-α), 7.73 (d, 1H, CH-β), 8.87 (s, 1H, quinoline), 10.87 (s, 1H, NH, Exchange with D_2O) MS (scanining mode ES^+) m/z: 463 (M^+).
Similarily the other compounds of the series were prepared.

Synthesis of 2-(2-Chloroquinilino-3'-yl)-3-(4'-toulylsulphonyl aminophenyl)-2,3-dihydro-1,5-benzothiazepine (4a).

A mixture of 3-(2-chloroquinolin-3-yl)-1-(4-(tosylamino)phenyl)prop-2-en-1-one (0.01 mole) and 2-aminothiophenol (0.011 mole) was dissolved in ethanol (50 mL). To this few drops of piperdine were added and the content was refluxed for 4 h. It was then acidified with glacial acetic acid (10 mL) and subsequently refluxed for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was left overnight at room temperature. Then reaction mixture was poured on crushed ice and the obtained solid was filtered and crystallized from ethanol.

Yield 75%, mp 113-115 ^oC. IR (KBr) cm^{-1}: 3269, 1605, 1573, 1341 and 1162, 1247. 749. ^{1}HNMR (DMSO-d_6) δ: 2.32 (S, 3H, CH_3), 2.88, 3.46 (dd, 2H, CH_2) 5.27 (m, 1H, CH), 7.09 to 8.05 (m, 16H, Ar-H).

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8.21 (s, 1H, quinoline) MS. (scanining mode ES^+) m/z: 571 (M^+).
Other compounds (**4b-e**) were similarily prepared.

Synthesis of 3-(4'-tosylaminophenyl)-5-(2'-chloroquinolin-3-yl)-4,5-dihydro isoxazolines (5a).

A mixture of 3-(2-chloro-substitutedquinolin-3-yl)-1-(4-(tosylamino)phenyl)prop-2-en-1-one (0.01 mole), potassium hydroxide (0.02 mole) and hydroxylamine hydrochloride (0.02 mole) in ethanol (50 mL) was refluxed for 7 h. The reaction was monitored by TLC. After completion of the reaction, it was poured on crushed ice and acidified with acetic acid. The obtained solid was filtered, washed with water and crystallized from ethanol.

Yield 72%, mp 134-136 ^oC, IR (KBr) cm^{-1}: 3266, 1601, 1336 and 1160, 1298, 1091. ^{1}HNMR (DMSO-d_6) δ: 2.32 (S, 3H, CH_3), 3.99, 4.07 (dd, 2H, CH_2), 6.04 (m, 1H, CH), 7.01 to 8.40 (m, 12H, Ar-H), 8.54 (s, 1H, quinoline).11.03 (s, 1H, NH exchange with D_2O). MS (Scanning mode ES^+) m/z: 478 (M^+).
The other products (**5b-e**) of the series were similarily obtained.

Conclusions

We have synthesized a series of new chalcones, 1,5-benzothiazepines and isoxazolines containing bioactive heteryl pharmacophores such as quinoline and sulphonamide using convenient methods. The intermediate sulphonamide was synthesized by improved synthetic route. The antibacterial activity of 1.5-benzothiazepines and isoxazolines was evaluated. Among them 1,5-benzothiazepines (4a-d) displayed notable antibacterial activity.

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