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Synthesis of New Chalcones and 1,5-Benzothiazepines Containing Quinolino and Thiazolyl Pharmacophores

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ABSTRACT

*A series of new 2-(2-chloro-substitutedquinilino-3-yl)-4-(2'-phenylthiazol-5'-yl)-2,3-dihydro-1,5-benzothiazepines (**4a-f**) have been prepared by carrying cyclocondensation of new 3-(2-chloro-substitutedquinolin-3-yl)-1-(4-metyl-2-phenylthiazol-5-yl)prop-2-en-1-ones (**3a-f**) and 2-aminothio phenol in DMF. Intermediate chalcones were obtained from the interaction of 2-chloro-substitutedquinoline-3-carbaldehyde (**1**) and 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (**2**) in ethanol, using claisen condensation. The synthesized 1,5-benzothiazepines **4a**, **4c**, **4d** and **4f** have been screened for their antibacterial activity against Staphylococcus aureus, Bacillus subtilis and Escherichia coli.*

Keywords : 5-Acetylthiazole, 2-chloro-3-formylquinoline, chalcones, 1,5-benzothiazepines, antibacterial activity.

INTRODUCTION

Chalcones, find great use in organic synthesis. The chalcones are useful building blocks for five and seven membered heterocycles. Naturally occurring and synthetic chalcones have shown promising biological activities. The presence of enone functional its in the chalcones help them to display various pharmacological activities [1-3].
1,5-Benzothiazepine nucleus has been well proved as illustrated by a large number of patents chemotherapeutic covering their utilities. A number of biological activities such as anticonvulsant [4] Ca^{+2} channel antagonist [5], antianginal [6], anti-HIV [7] squalene synthetase inhibitor [8], V_2 arginine vasoperssion receptor antagonist [9], HIV-1 reverse transcriptase inhibitor [10] etc. have been displayed by 1,5-benzothiazepines.

Thiazole ring system is a useful structural element in medicinal chemistry and has broad application in the drug development. Thiazole and thiazolidone nuclei exhibit a number of biological properties, such as antimicrobial [11], antiprotozoa [12], antitubercular [13] and anticancer [14]. Quinoline ring system also play vital role in nature due to their wide range of biological activities and industrial importance. They have been used to synthesize various fused heterocyclic ring systems, which also show a wide range of pharmacological activities [15-17].

In view of these observations, great importance of these heteryl nuclei and in continuation of our work on biologically active heterocycles [18] here in the present work an attempt has been made to synthesize new chalcones and 1,5-benzothiazepines incorporating heteryl pharmacophores such as quinoline and thiazole in a single molecular frame work, with the hope to obtained new molecules with enhanced biological activity.

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}H NMR was measured on Bruker DRX-300, 300 MHZ FT NMR with low and high temperature in DMSO-d_6 using TMS as internal reference. Mass spectra were recorded on an Ieo SX 102/DA-600 mass spectrometer.

General procedure for the synthesis of 3-(2-Chloro-substitutedquinoline-3-yl)-1-(4-methyl-2-Phenylthiazole-5-yl)prop-2-en-1-ones (3a-f). A mixture of 1-(4-Methyl-2-Phenylthiazole-5-yl) ethanone (0.002 mol) and potassium hydroxide (0.0058 mol) was dissolved in ethanol (15 mL). To this solution 2-chloro-substitutedquinoine-3-carbaldehydes (0.002 mol) was added in portion at 0-5 ^{o}C with constant stirring. To this reaction mass 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 ^{o}C. It was then allowed to stand at room temperature for overnight. The reaction progress was monitored by TLC.Then the reaction mass was poured on crushed ice and neutralized by glacial acetic acid. The solid appeared was filtered, washed with cold water and crystallized from ethanol: ethyl acetate.

Compound (3a) Yield 75 %, mp 185-187 ^{o}C. IR (KBr) cm^{-1}: 3067, 2902, 1654, 1619, 1594, 1563, 1240, 683. ^{1}H NMR (DMSO-d_6) δ: 2.67 (s, 3H, CH_3), 7.52 (m, 5H, Ar-H), 7.60 (d, 1H,CH-α), 7.75 (d, 1H, CH-β), 7.94 (m, 4H, quinoline), 8.58 (s, 1H, quinoline). MS (m/z): 390 (M^+), 392 (M^+ +2).

Compound (3c) Yield 78 %, mp 173-175 ^{o}C. IR (KBr) cm^{-1}: 3065, 2894, 1651, 1621, 1593, 1565, 1257, 685. ^{1}H NMR (DMSO-d_6) δ: 1.53 (t, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.18 (q, 2H, CH_2),7.52 (m, 5H, Ar-H), 7.60 (d, 1H, CH-α), 7.75 (d, 1H, CH-β), 7.49 (d, 3H, quinoline), 8.41 (s, 1H, quinoline). MS (m/z): 434 (M^+), 436 (M^+ +2).

Compound (3d) Yield 65 %, mp 177-179 ^{o}C. IR (KBr) cm^{-1}: 3068, 2909, 1658, 1620, 1594, 1562, 1255, 684. ^{1}H NMR (DMSO-d_6) δ: 2.67 (s, 3H, CH_3), 7.52 (m, 5H, Ar-H), 7.60 (d, 1H, CH-α), 7.75 (d, 1H, CH-β), 7.95 (m, 3H, quinoline), 8.59 (s, 1H, quinoline). MS (m/z): 424 (M^+), 426 (M^+ +2), 428 (M^+ +4).

Compound (3f) Yield 72 %, mp 160-162 ^{o}C. IR (KBr) cm^{-1}:3057, 2911, 1652, 1618, 1594, 1569, 1253, 682. ^{1}H NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 7.52 (m, 5H, Ar-H), 7.60 (d, 1H, CH-α), 7.75 (d, 1H, CH-β), 7.76 (m, 3H, quinoline), 8.55 (s, 1H, quinoline). MS (m/z): 404 (M^+), 406 (M^+ +2).

General procedure for the synthesis of 2-(2-Chloro-substitutedquinolino-3-yl)-4-(2$^{'}$-phenyl thiazol-5$^{'}$-yl)-2,3-dihydro-1,5-benzothiazepines (4a-f). A mixture of 3-(2-chloro-substituted quinolino-3-yl)-1-(4-methyl-2-phenylthiazol-5-yl)prop-2-en-1-ones (0.002 mol) and 2-amino thiophenol (0.0022 mol) was dissolved in DMF (10 mL). A few drops of piperidine were added to the solution and it was then refluxed for 4 h. It was then acidified with glacial acetic acid (2 mL) and reaction mixture was further refluxed for 2 h. The progress of the reaction was monitored by TLC. After completion the reaction mixture was left overnight at room temperature. Then the reaction mass was poured in ice cold water and the obtained solid was filtered. The crude was crystallized form EtOH: DMF.
Compound (4a) yield 65%, mp 158-160˚C, IR (KBr) cm^{-1}: 3059, 2923, 1621, 1605, 1580, 1562, 760. ^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 2.70, 2.74 (dd, 2H, CH_2), 3.98 (m, 1H, CH) and 6.80 to 8.26 (m, 13H, Ar-H), 8.68 (s, 1H, quinoline). MS (scanning mode ES$^+$) m/z: 498 (M^+), 500 (M^+ +2).

Compound (4c) yield 70%, mp 137-139˚C, IR (KBr) cm^{-1}: 3061, 2918, 1620, 1602, 1579, 1566, 758. ^{1}H NMR (DMSO-d_6) δ: 1.55 (t, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.73, 2.76 (dd, 2H, CH_2), 3.99 (m, 1H, CH), 4.19 (q, 2H, CH_2) and 6.73 to 8.09 (m, 12H, Ar-H), 8.61 (s, 1H, quinoline). MS (scanning mode ES$^+$) m/z: 542 (M^+), 544 (M^+ +2).

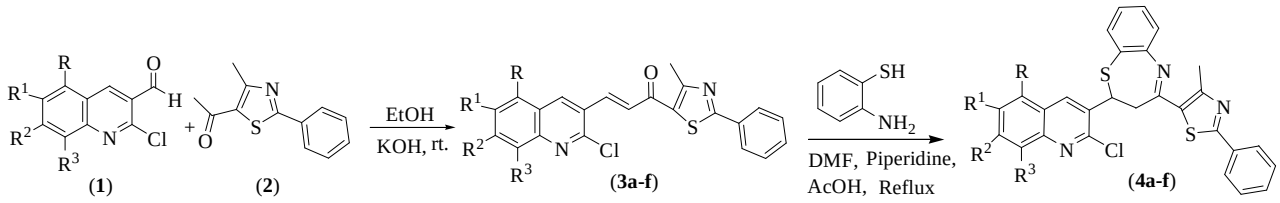
Compound (4d) yield 62%, mp 133-132˚C, IR (KBr) cm^{-1}: 3059, 2924, 1621, 1605, 1581, 1565, 760. ^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 2.70, 2.73 (dd, 2H, CH_2), 3.98 (m, 1H, CH), and 6.80 to 8.10 (m, 12H, Ar-H), 8.68 (s, 1H, quinoline). MS (scanning mode ES$^+$) m/z: 532 (M^+), 534 (M^+ +2), 536 (M^+ +4).

Compound (4f) yield 72%, mp 151-153˚C, IR (KBr) cm^{-1}: 3058, 2923, 1620, 1604, 1583, 1564, 760. ^{1}H NMR (DMSO-d_6) δ: 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.71, 2.75 (dd, 2H, CH_2), 3.98 (m, 1H, CH), and 6.76 to 8.10 (m, 12H, Ar-H), 8.65 (s, 1H, quinoline). MS (scanning mode ES$^+$) m/z: 512 (M^+). 514 (M^+ +2).

RESULTS AND DISCUSSION

The key intermediates, 2-chloro-substitutedquinoline-3-carbaldehydes (**1**) were synthesized using Vilsmeier-Haack reagent following literature [19]. Procedure using Hantzsch method [20] we have synthesized 1-(4-methyl-2-phenylthiazol-5yl) ethanone (**2**) in good yield by condensing α-haloketones with thiobenzamide. Compounds (**3a-f**) were prepared by a carrying Claisen Schmidt condensation of 2-chloro-substitutedquinoline-3-carbaldehydes and 5-acetylthiazole in alcoholic KOH. Using this method we obtained excellent yields of the new chalcones (**3a-f**). The

cyclocondensation of compound (**3a-f**) with 2-aminothiophenol when carried in DMF gave good yields of the titled 1,5-benzothiazepines (**4a-f**). The reaction sequence is outlined in **Scheme 1**. The new compounds have been characterized by IR, ^{1}H NMR and mass analyses.



Scheme 1 Synthetic routes of chalcones and 1,5-benzothiazepines.

Table 1. Physical data of chalcones (3a-3f).

Products	R	R^1	R^2	R^3	Yield[a] (%)	Mp (^{o}C)
3a	H	H	H	H	75	185-187
3b	H	H	CH_3	H	72	192-194
3c	H	OCH_2CH_3	H	H	78	173-175
3d	H	Cl	H	H	65	177-179
3e	H	H	H	CH_3	70	170-172
3f	H	CH_3	H	H	72	160-162

[a] *Isolated yield.*

Table 2. Physical data of 1.5-benzothiazepines (4a-4f).

Products	R	R^1	R^2	R^3	Yield[a] (%)	Mp (^{o}C)
4a	H	H	H	H	65	158-160
4b	H	H	CH_3	H	68	139-141
4c	H	OCH_2CH_3	H	H	70	137-139
4d	H	Cl	H	H	62	130-132
4e	H	H	H	CH_3	75	118-120
4f	H	CH_3	H	H	72	151-153

Characteristic absorption of (**3a**) as one of the representative products (**3a-f**) has been presented bellow MS (m/z): 390 (M^+), 392 (M^+ +2). IR (KBr) cm^{-1} 3067 (C-H, str. aromatic), 2902 (C-H, str. aliphatic), 1654 (C=O, str. lowering of normal carbonyl frequency is due to presence α,β-unsaturation and heteryl ring system), 1619 (C=C, str. aromatic), 1594 (C=N, str. quinoline), 1563 (C=N, thiazole), 683 (C-S-C, str.thiazole).^{1}H NMR (DMSO-d_6) δ: 2.67 (s, 3H, CH_3), 7.52 (m, 5H, Ar-H), two vinylic protons 7.60 (d, 1H,CH-α), 7.75 (d, 1H, CH-β), 7.94 (m, 4H, quinoline), 8.58 (s, 1H, quinoline).Spectra data of (**4a**) as one of the representative products (**4a-f**) MS (scanning mode ES^+) (m/z): 498 (M^+), 500 (M^+ +2). IR (KBr) cm^{-1} 3059 (C-H, str. aromatic), 2923 (C-H, str. aliphatic), 1621 (C=C, str. aromatic), 1605 (C=N, str. 1,5-benzothiazepine), 1580 (C=N, str. quiniline), 1562 (C=N, str. thiazole), 760 (C-S-C, str. 1,5-benzothiazepine).^{1}H NMR (DMSO-d_6) δ: 2.47 (s, 3H, CH_3), 2.70, 2.74 (dd, 2H, methylene protons of 1,5-benzothiazepine), 3.98 (m, 1H, methine proton of 1,5-benzothiazepine) and 6.80 to 8.26 (m, 13H, aromatic protons), 8.68 (s, 1H, quinoline).

Antibacterial activity of 1.5-benzothiazepines

The synthesized compounds **4a**, **4c**, **4d** and **4f** were screened *in vitro* for their antibacterial activities against three strains of bacteria (Staphylococcus aureus, Bacillus subtilis and Escherichia coli). Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 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**, **4c**, **4d** and **4f** are presented in **Table 3a-c** as the minimal inhibitory concentration (MIC µg).It has been observed that the compounds exhibited interesting antibacterial activity however, with degree of variation. The compounds **4c** and **4d** were found to be moderate to good activity against S. aureus and E. coli. They were also found most active against B. subtilis. The compound **4f** displayed notable activity against B. subtilis.

Table 3a: antibacterial activity against B. substilis

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC
4a	0	0	0	0	0	0	> 2
4c	0.3	0.8	1.1	1.3	1.4	1.6	0.0625
4d	1	1.3	1.4	1.5	1.8	2.2	< 0.0625
4f	0	0	0	0.6	1	1.4	< 0.05
	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 3b: 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
4a	0	0	0	0	0	0	> 2
4c	1.1	1.5	1.6	1.7	1.9	2.1	< 0.0625
4d	0	0	0	0	0.8	1.2	1
4f	0	0	0	0	0	1	2
	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 3c: antibacterial activity against E.col

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC
4a	0	0	0	0	0	0	> 2
4c	0	0	1.1	1.3	1.4	1.6	0.25
4d	0	0	0.8	1.1	1.6	2	2
4f	0	0	0	0	0	1.4	2
	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	MIC µg
Streptomycin	1	1.7	1.8	1.1	1.2	2.6	< 25
Penicillin	0	0.3	0.8	1.5	1.6	2.2	50

CONCLUSION

We have synthesized a series of new chalcones and 1,5-benzothiazepines containing bioactive heteryl pharmacophores such as thiazole and quinoline using convenient method. The antibacterial activity of representative compounds was evaluated. Among them, compounds 4c & 4d showed a moderate degree of antibacterial activity.

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REFERENCES

[1] A Jurasek; V Knoppava; M Danderova; J Kovac; L Reinprech. *Telrahedron*, **1978**, 34, 1833-1836.
[2] R De Vincenzo; C Ferlini; M Distefano; C Gaggini; A Riva; E Bombardelli; P Morazzoni; P Valenti; F Belluti; F O Ranelletti; S Mancuso; G Scambia. *Cancer Therapy Pharmacol*, **2000**, 46, 305-312.
[3] K B Raut; H Wender. *J. Org. Chem*., **1960**, 25, 50-52.
[4] G D Sarro; A Chimirri; A D Sarro; R Gitto; S Grasso; M Zappala. *Eur. J. Med. Chem*., **1995**, 30, 925-929.
[5] (a) Y Shinichi; M Yoshikazu; M Katsuji; I Yoshinori; O Yasuhiko; Y Ryuzo; N Tadashi; S Hiroyasu. *J. Org. Chem*., **1996**, 61, 8586-8590; (b) J Kruokawa; S Adachi-Akahane; T Nagao. *Eur. J. Pharmacol*. **1997**, 325, 229-236.
[6] O Miyata; S Tetsuro ; N Ichiya; N Takeaki. *Tetrahedron*, **1997**, 53, 2421-2438.
[7] G Garandolini; L Perioli; V Ambrogi. *Eur. J. Med. Chem*., **1999**, 34, 701-709.
[8] X Yang; L Buzon; E Hamanaka; K K-C Liu. *Tetrahedron*, **2000**, 11, 4447-4450.
[9] M J Urbanski; R H Chen; K T Demarest; J Gannet; R Look; E Ericson; W V Murray; P J Rybezynski; X Zhang. *Bioorg. Med. Chem. Lett*., **2003**, 13, 4031-4034.
[10] R Di Santo; R Costi. *Farmaco*, **2005**, 60, 385-392.
[11]C V Kavitha; S N Swamy; K Mantelingu; S Doreswamy; M A Sridhar; J S Prasad; K S Rangappa. *Bioorg. Med. Chem*., **2006**, 14, 2290-2299.
[12]R A Tapia; L Alegria; C D Pessoa; C Salas; M J Cortes; J A Cortes; M E Sarciron; F Pautet; N Walchshofer; H Fillion. *Bioorg. Med. Chem*., **2003**, 11, 2175-2182.
[13]S R Pattan; A A Bukitagar; K G Bhat; J S Pattan; B S Kittur; A B Khade. *Indian Drugs*, **2007**, 44, 689-692.
[14] P Vicini; A Geronikaki; M Incerti; B Busonera; G Poni; C A Cabras; P La Colla. *Bioorg. Med. Chem*., **2003**, 11, 4785-4789.
[15] A O Abbott; V R Bonnert; V M Caffrey; A P Cage; J A Cooke; K D Donald. *Tetrahedron*, **2002**, 58, 3185-3198.
[16] C B Ranu; A Hajra; S S Dey; U Jana. *Tetrahedron*, **2003**, 59, 813-819.
[17] P Helissey; S D Finck; S G Renault. *Eur. J. Org. Chem*. **2005,** 2, 410-415.
[18](a) V B Jagrut; P D Netankar; D V Jawale; R A Mane; W N Jadhav. *Bull. Korean. Chem. Soc*., **2009**, 30, 2812-2814; (b) V B Jagrut; U R Pratap; R A Mane; W N Jadhav. *Chemistry & Biology Interface*, **2011**, 2, 185-191.
[19] A Srivastava; R M Singh. *Ind. J. Chem.*, **2005**, 44B, 1868-1875.
[20] A R Hantzsch; J H Weger. *Ber. Dsch. Chem. Ges*., **1887**, 20, 3118-313