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Synthesis and Antifungal Potency of Novel 4-Aryl-2-(2,4-Dichlorophenyl)-1,4-Benzothiazepine Derivatives

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Abstract : An easy procedure for the synthesis of 1,4-benzothiazepines was described. The reaction of chalcones, **1a-g** and 2-aminothiophenol, **2** in the presence of catalytic amount of concentrated hydrochloric acid in methanol under reflux conditions produced 1,4-benzothiazepines in good yields. The synthesized new compounds were characterized by spectral studies and elemental analysis; and were screened *in vitro* for their antifungal activities against different fungi species.
Key words : Antifungal, chalcones, condensation, inhibition, MIC, thiazepine.

Introduction

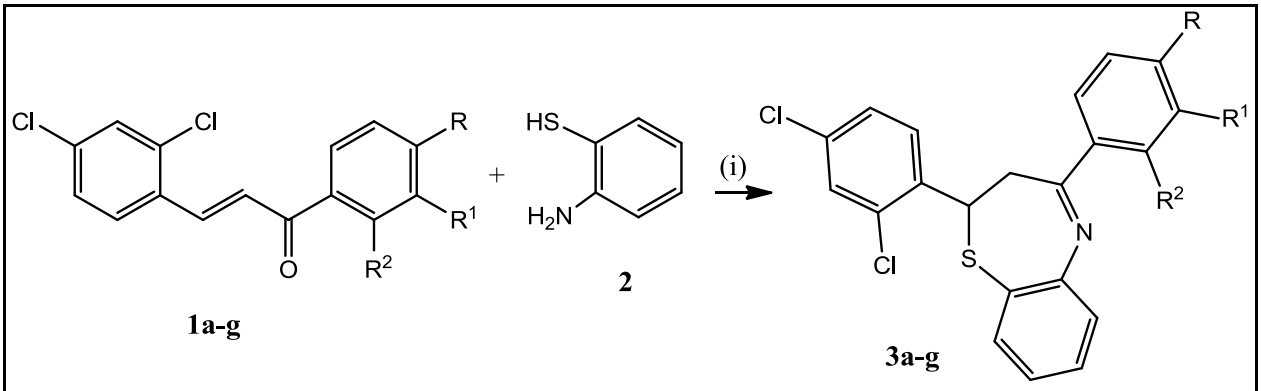
Chalcones were regarded as the central core for the construction of variety of bioactive molecules, such as benzothiazepine,[1-3] pyrazoles,[4] isoxazoles[5]etc. 1, 4-Benzothiazepine skeleton is an important moiety that has been widely used as building block for pharmaceutical agents. The broad spectrum of clinical importance and commercial success associated with benzothiazepines has led to their recognition in the medicinal chemistry.[6-9] The reaction of 2'-aminoethyl-3,4-dimethoxyphenyl sulfide hydrochloride with acid chlorides produced the acid amides, which on ring closure with phosphoryl chloride furnished the 2,3-dihydro-l,4-benzothiazepine.[10] The one-pot reaction between 2-aminobenzo[d]isothiazol-3-one and alkyl propiolates in presence of triphenylphosphine leads to the corresponding alkyl 4-amino-5-oxobenzo[f][1,4]thiazepine-3-carboxylates.[11]

1, 4-Benzothiazepine derivatives are known to exhibit biological activities such as antioxidant,[12] antimicrobial[13] etc. In view of broad spectrum of synthetic and biological applications associated with 1,4-benzothiazepines, we herein report the synthesis and antifungal activity studies of series of new 1,4-benzothiazepine derivatives.

Materials and Methods

Melting points were determined by an open capillary tube method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates pre-coated with silica gel using solvent system ethyl acetate: dichloromethane (1:4 v/v). The spots were visualized under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrometer respectively. The solvent $CDCl_3$ with TMS as an internal standard was used to record the spectra. The chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrometer TOF mode. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyzer. Purification of compounds was done by column chromatography on silica gel (70-230 mesh Merck).

The required precursor chalcones, **1a-g** were prepared according to our earlier reported procedure. The cyclocondensation reaction of chalcones, **1a-g** with 2-aminothiophenol, **2** in the presence of few drops of concentrated hydrochloric acid in methyl alcohol under reflux conditions produced 1,4-benzothiazepine derivatives, **3a-g** in good yields. The schematic diagram for the synthesis of 1,4-benzothiazepines is outlined in **Figure-1**.



1 a) R=H, R^1=H, R^2=H; b) R=F, R^1=H, R^2=H; c) R=Cl, R^1=H, R^2=H;
d) R=OCH_3, R^1=H, R^2=H; e) R=OCH_3, R^1=H, R^2=H; f) R=H, R^1=OCH_3, R^2=H;
g) R=H, R^1=H, R^2=OCH_3**.**
Reagents and condition: (i) MeOH/HCl, reflux, 3h.

Figure. 1: Schematic diagram for the synthesis of benzothiazepine derivatives, 3a-g.

General procedure for the synthesis of 1,4-benzothiazepines, 3a-g: To a stirred solution of chalcones, **1a-g** (0.01 mol) and 2-aminothiophenol, **2** (0.01 mol) in methyl alcohol (15 mL), concentrated hydrochloric acid (7-8 drops) were added. The mixture was refluxed for 3-4 h and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured in to ice cold water; solid separated was filtered, washed with ice cold water and dried. The products were purified column chromatography using silica gel (60-120 mesh) and ethyl acetate : n-hexane (1:4 v/v) as eluent.

2-(2,4-Dichlorophenyl)-4-phenyl-2,3-dihydrobenzo[b][1,4]thiazepine, **3a:** Obtained from 3-(2,4-dichlorophenyl)-1-phenylprop-2-en-1-one, **1a** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 71% yield, m.p. 109–111°C. ^{1}H NMR: δ 1.870-1.969 (dd, 1H, *J= 6.7, 13.0Hz*, C_3-H_a), 2.210-2.345 (dd, 1H, *J= 7.0, 12.4Hz*, C_3-H_b), 3.976-4.172 (dd, 1H, *J= 7.1, 14.0Hz*, C_2-H), 7.235–7.950 (m, 12H, Ar–H); ^{13}C NMR: δ 40.54 (1C, C-3), 44.80 (1C, C-2), 117.63 (1C), 125.66 (1C), 126.90 (1C), 127.02 (1C), 128.12 (2C), 128.60 (2C), 130.16 (1C), 130.74 (1C), 131.50 (1C), 133.41 (1C), 133.96 (1C), 134.50 (1C), 136.92 (1C), 137.52 (1C), 138.14 (1C), 156.40 (1C), 161.86 (1C, C-4). MS *m/z*: 387 (M+4, 13), 385 (M+2, 67), 383 (M+, 100); Anal. calcd. for $C_{21}H_{15}Cl_2NS$ (%): C, 65.63; H, 3.93; N, 3.64; Found: C, 65.51; H, 3.77; N, 3.43.

2-(2,4-Dichlorophenyl)-4-(4-fluorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepine, **3b:** Obtained from 3-(2,4-dichlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one, **1b** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 75% yield. ^{1}H NMR: δ 1.860-1.966 (dd, 1H, *J= 7.0, 13.9Hz*, C_3-H_a), 2.223-2.354 (dd, 1H, *J= 7.0, 14.0Hz*, C_3-H_b), 3.990-4.206 (dd, 1H, *J= 7.1, 14.0Hz*, C_2-H), 7.228–7.960 (m, 11H, Ar–H); ^{13}C NMR: δ 39.86 (1C, C-3), 44.44 (1C, C-2), 115.61 (2C), 117.40 (1C), 125.54 (1C), 126.43 (1C), 125.40 (1C), 129.65 (2C), 127.77 (1C), 130.42 (1C), 130.95 (1C), 133.38 (1C), 133.70 (1C), 134.46 (1C), 134.90 (1C), 138.14 (1C), 156.30 (1C), 162.35 (1C, C-4), 164.62 (1C). MS *m/z*: 405 (M+4, 13), 403 (M+2, 68), 401 (M+, 100); Anal. calcd. for $C_{21}H_{14}Cl_2FNS$ (%): C, 62.69; H, 3.51; N, 3.48; Found: C, 62.60; H, 3.42; N, 3.39.

4-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepine, **3c:** Obtained from 3-(2,4-dichlorophenyl)-1-(4-chlorophenyl)prop-2-en-1-one, **1c** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 66% yield. ^{1}H NMR: δ 1.852-1.960 (dd, 1H, *J= 8.3, 16.1Hz*, C_3-H_a), 2.218-2.342 (dd, 1H, *J= 7.1, 15.5Hz*, C_3-H_b), 3.986-4.184 (dd, 1H, *J= 7.3, 14.4Hz*, C_2-H), 7.227–7.946 (m, 11H, Ar–H); ^{13}C NMR: δ 40.09 (1C, C-3), 44.50 (1C, C-2), 116.62 (1C), 125.66 (1C), 126.20 (1C), 127.10 (1C), 128.08 (2C), 128.60 (2C), 130.24 (1C), 130.55 (1C), 133.40 (1C), 133.98 (1C), 134.24 (1C), 135.44 (1C), 136.50 (1C), 137.80 (1C), 138.32 (1C),

156.10 (1C), 162.94 (1C, C-4).Anal. calcd. for $C_{21}H_{14}Cl_3NS$ (%): C, 60.23; H, 3.37; N, 3.34; Found: C, 60.12; H, 3.24; N, 3.20.

***2-(2,4-Dichlorophenyl)-4-(4-methylphenyl)-2,3-dihydrobenzo[b][1,4]thiazepine,* 3d:** Obtained from 3-(2,4-dichlorophenyl)-1-(4-methylphenyl)prop-2-en-1-one, **1d** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 80% yield. ^{1}H NMR: δ 1.861-1.956 (dd, 1H, *J= 7.0, 12.1Hz*, C_3-H_a), 2.230-2.336 (dd, 1H, *J= 7.0, 12.5Hz*, C_3-H_b), 2.350 (s, 3H, CH_3), 3.996-4.187 (dd, 1H, *J= 7.6, 14.0Hz*, C_2-H), 7.234–7.950 (m, 11H, Ar–H); ^{13}C NMR: δ 20.40 (1C), 40.26 (1C, C-3), 44.80 (1C, C-2), 114.65 (2C), 117.34 (1C), 125.63 (1C), 126.00 (1C), 127.22 (1C), 128.54 (2C), 129.46 (1C), 130.50 (2C), 133.43 (1C), 133.98 (1C), 134.35 (1C), 137.21 (1C), 137.55 (1C), 154.48 (1C), 161.88 (1C, C-4), 163.09 (1C). MS *m/z*: 401 (M+4, 13), 399 (M+2, 68), 397 (M+, 100); Anal. calcd. for $C_{22}H_{17}Cl_2NS$ (%): C, 66.33; H, 4.30; N, 3.52; Found: C, 66.20; H, 4.16; N, 3.39.

***2-(2,4-Dichlorophenyl)-4-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepine,* 3e:** Obtained from 3-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one, **1e** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 78% yield; ^{1}H NMR: δ 1.868-1.972 (dd, 1H, *J= 7.1, 13.3Hz*, C_3-H_a), 2.202-2.330 (dd, 1H, *J= 7.8, 15.0Hz*, C_3-H_b), 3.850 (s, 3H, OCH_3), 3.984-4.190 (dd, 1H, *J= 8.0, 14.5Hz*, C_2-H), 7.230–7.952 (m, 11H, Ar–H); ^{13}C NMR: δ 40.20 (1C, C-3), 44.72 (1C, C-2), 55.49 (1C), 114.60 (2C), 117.42 (1C), 125.60 (1C), 126.12 (1C), 127.10 (1C), 128.66 (2C), 129.61 (1C), 130.51 (2C), 133.46 (1C), 133.90 (1C), 134.40 (1C), 137.20 (1C), 137.58 (1C), 154.41 (1C), 161.90 (1C, C-4), 163.30 (1C). MS *m/z*: 417 (M+4, 14), 415 (M+2, 66), 413 (M+, 100); Anal. calcd. for $C_{22}H_{17}Cl_2NOS$ (%): C, 63.77; H, 4.14; N, 3.38; Found: C, 63.70; H, 4.05; N, 3.19.

***2-(2,4-Dichlorophenyl)-4-(3-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepine,* 3f:** Obtained from 3-(2,4-dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one, **1f** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 75% yield; ^{1}H NMR: δ 1.857-1.966 (dd, 1H, *J= 6.2, 13.0Hz*, C_3-H_a), 2.200-2.327 (dd, 1H, *J= 7.0, 12.9Hz*, C_3-H_b), 3.846 (s, 3H, OCH_3), 3.981-4.177 (dd, 1H, *J= 6.9, 14.0Hz*, C_2-H), 7.226–7.944 (m, 11H, Ar–H); ^{13}C NMR: δ 40.18 (1C, C-3), 44.77 (1C, C-2), 55.55 (1C), 114.84 (2C), 117.60 (1C), 125.63 (1C), 126.22 (1C), 127.35 (1C), 128.60 (2C), 129.74 (1C), 130.51 (2C), 133.46 (1C), 133.95 (1C), 134.75 (1C), 137.00 (1C), 137.88 (1C), 154.47 (1C), 161.66 (1C, C-4), 163.09 (1C). MS *m/z*: 417 (M+4, 13), 415 (M+2, 67), 413 (M+, 100); Anal. calcd. for $C_{22}H_{17}Cl_2NOS$ (%): C, 63.77; H, 4.14; N, 3.38; Found: C, 63.66; H, 4.01; N, 3.22.

***2-(2,4-Dichlorophenyl)-4-(2-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepine,* 3g:** Obtained from 3-(2,4-dichlorophenyl)-1-(2-methoxyphenyl)prop-2-en-1-one, **1g** (10 mmol) and 2-aminothiophenol, **2** (10 mmol) in 80% yield. ^{1}H NMR: δ 1.860-1.966 (dd, 1H, *J= 7.5, 13.1Hz*, C_3-H_a), 2.210-2.338 (dd, 1H, *J= 6.5, 13.4Hz*, C_3-H_b), 3.853 (s, 3H, OCH_3), 3.980-4.178 (dd, 1H, *J= 8.4, 13.2Hz*, C_2-H), 7.235–7.958 (m, 11H, Ar–H); ^{13}C NMR: δ 40.46 (1C, C-3), 44.66 (1C, C-2), 55.45 (1C), 114.97 (2C), 117.33 (1C), 125.45 (1C), 126.42 (1C), 127.09 (1C), 128.48 (2C), 129.58 (1C), 133.41 (1C), 130.34 (2C), 133.78 (1C), 134.44 (1C), 137.16 (1C), 137.55 (1C), 154.39 (1C), 161.76 (1C, C-4), 163.76 (1C). MS *m/z*: 417 (M+4, 13), 415 (M+2, 65), 413 (M+, 100); Anal. calcd. for $C_{22}H_{17}Cl_2NOS$ (%): C, 63.77; H, 4.14; N, 3.38; Found: C, 63.68; H, 4.00; N, 3.20.

Results and Discussion

Structure proof of synthesized compounds, **3a-g** were provided by ^{1}H NMR, ^{13}C NMR, Mass spectral studies and elemental analysis. The structural assignments were made by spectral analysis by considering 2-(2,4-dichlorophenyl)-4-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepine, **3e** as the representative compound among the series. In ^{1}H NMR spectra, two methylene protons designated as C_3-H_a and C_3-H_b of the newly formed benzothiazepine ring are diastereotopic and exhibit typical ABX spin. The C_3-H_a, C_3-H_b and C_2-H protons appeared as a doublet of doublets. The doublet of doublet for C_3-H_a appears at δ 1.868-1.972 (*J= 7.1, 13.3Hz*) ppm; doublet of doublet for C_3-H_b appears at δ 2.202-2.330 (*J=7.8, 15.0Hz*) ppm; and that of C_2-H appears at δ 3.984-4.190 (*J=8.0, 14.5Hz*) ppm. Among C_3-H_a, C_3-H_b and C_2-H protons, C_2-H is the most deshielded due to its close proximity to aromatic ring and sulphur atom. C_2-H couples not only with C_3-H_a but also with C_3-H_b and appears as doublet of doublet instead of a triplet. A signal appears as singlet for three protons at δ 3.850 ppm was assigned to OCH_3 protons. An array of signals appears as multiplet for eleven protons at δ 7.230–7.952 ppm were assigned to aromatic protons.

In ^{13}C NMR spectrum, compound **3e** showed signals at δ 40.20, 44.72 and 161.90 ppm due to C-3, C-2 amd C-4 carbons of the benzothiazepine ring. A signal appeared at δ 55.49 ppm was assigned to OCH_3 carbon. An array of signals appeared for one carbon each at δ 117.42, 125.60, 126.12, 127.10, 129.61, 133.46, 133.90,

134.40, 137.20, 137.58, 154.41, 163.30 and two carbon each at δ 114.60, 128.66, 130.51 ppm were assigned to aromatic carbons. Compound **3e** showed molecular ion peaks at m/z 417 (M+4, 14), 415 (M+2, 66) and 417 (M+, 100) corresponding to its molecular mass. Further, it showed satisfactory analytical data, and supports the structure of the compound. The remaining compounds of the synthesized series showed similar and consistent pattern signals in their respective spectra, which strongly supports the structure proof of the compounds.

Antifungal activity

Antifungal activities of synthesized compounds **3a-g** were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method.[14] The compounds were screened for their antimicrobial activities against fungi species *Candila albicans*, *Aspergillus nigar* and *Aspergillus flavus*. The experiments were carried out in triplicate; the results were taken as a mean of three determinations. The antibiotic nystatin was used as a positive control. The results of minimum inhibitory concentrations (MIC's) were summarized in **Figure 1**.

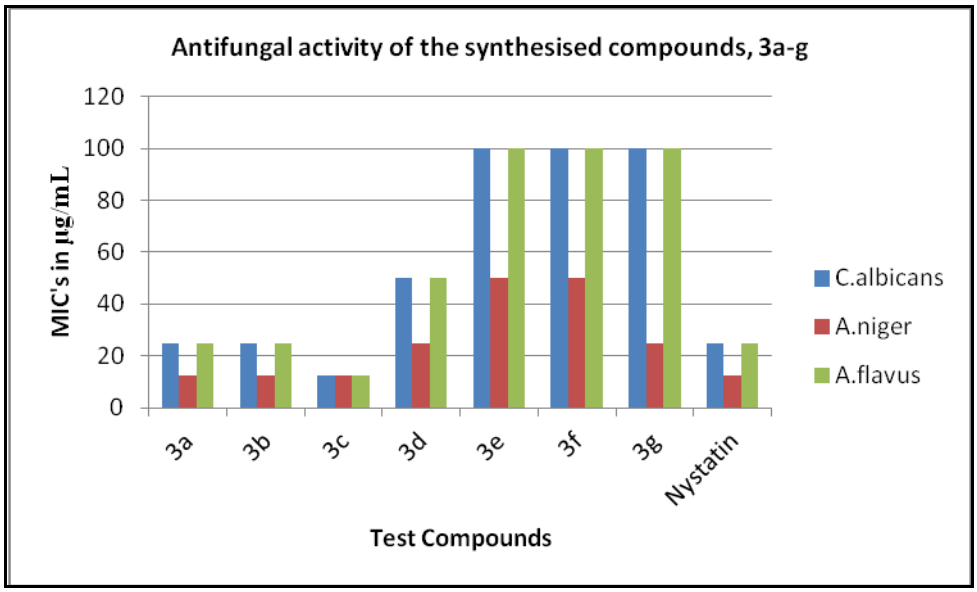


Figure 1: Minimum inhibitory concentrations (in µg/mL) of the synthesized compounds 3a-g against fungal stains; results are expressed as mean of three determinations (n=3).

The synthesized 1,4-benzothiazepines, **3a-g** exerted a wide range of *in vitro* antifungal activities against the tested fungi species. Preliminary investigation results of the study reveals that, amongst the series, compound **3c** having chloro substitutions in both the aromatic rings exhibited excellent inhibition against all the organisms. Compounds, **3a** and **3b** showed promising antifungal susceptibilities, **3d** having methyl substitution in one of the aromatic ring found moderately active against the tested organisms. The remaining compounds of the series, **3e**, **3f** and **3g** having methoxy substitutions displayed poorer activities in comparison with the standard.

Conclusions

The reaction described represents an easy route for the synthesis of 1,4-benzothiazepine derivatives. Preliminary studies on the antifungal activities of the synthesized 1,4-benzothiazepines reveals that some of the synthesized series of compounds acts as a potential antifungal agents, in particular 2-(2,4-dichlorophenyl)-4-(4-chlororophenyl)-2,3-dihydrobenzo[b][1,4]thiazepine, **3c** can be used as a potent antifungal agent against the tested organisms.

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