One-pot multi-component synthesis of 4-substituted thiazole Schiff base derivatives and their antibacterial activity

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A series of 4-substituted thiazole Schiff base derivatives (6a-h, 7a,b and 8a,b) have been synthesized via one pot multi-component condensation of 1-tetralone derivatives with thiosemicarbazide and 4-substituted phenacyl bromides/3-(2-bromoacetyl)-2H-chromen-2-one/2-(2-bromoacetyl)-3H-benzo[f]chromen-3-one under conventional heating in absolute ethanol using catalytic amount of acetic acid with good yields. All the synthesized compounds have been characterized by their IR, 1H and 13C NMR, mass spectra and elemental analyses and also assessed for their antibacterial activity against both Gram positive and Gram negative bacterial strains. Compounds 6h, 7a, 7b, 8a and 8b have shown excellent activity against tested bacterial strains when compared to standard drug Gentamicin.

Keywords: Conventional method, 2,4-disubstituted thiazoles, in vitro antibacterial evaluation, multi-component condensation

Nowadays for the synthesis of biologically active heterocyclic compounds, multi-component reactions (MCRs) are one of the best approaches in organic synthesis, where in three or more reactants are involved at once in a one pot method. When compared with multi step reactions, multi-component reactions have several advantages like high atom-economy, structural diversity, operational simplicity, and lack of waste products, etc. Similarly, the compounds possessing azomethine group (−C=N−) in the structure are known as Schiff bases, which have gained importance in medicinal chemistry because of their physiological and pharmacological properties. In the past, Schiff bases were reported as antibacterial, antifungal, anticancer and antiviral agents. On the other hand, compounds which incorporated thiazole motif have shown prominent medicinal value due to their potential chemotherapeutic, fungicidal, antiviral and antidiuretic properties. Thiazoles and their derivatives also exhibit various biological activities such as antibacterial, antifungal, anti-inflammatory, antihypertensive, anti-HIV, antitumor, antifilarial and anticonvulsant activities. Many biologically active products, such as Ritonavir (anti-HIV drug), Bleomycin and Tiazofurin (antineoplastic agents), Nizatidine (antiulcer agent), Fanetizole and Meloxicam (anti-inflammatory agents), imidacloprid (insecticide) and penicillin (antibiotic) are some examples of thiazole bearing products.

In view of the pharmacological importance of thiazole Schiff bases and advantages of multi-component reactions and in continuation of our research interest in synthesis of antibacterial heterocyclic compounds, we have designed and synthesized a series of 4-substituted thiazole Schiff base derivatives by one pot multi-component synthesis. All the synthesized compounds have been evaluated for their antibacterial activity.

Results and Discussion

The title compounds 4-substituted thiazole Schiff base derivatives (6a-h and 7a, 7b and 8a, 8b) were synthesized via one pot multi-component condensation of 1-tetralone derivatives (1a, 1b) and thiosemicarbazide (2) with various phenacyl bromides (3a-d) / 3-(2-bromoacetyl)-2H-chromen-2-one (4) / 2-(2-bromoacetyl)-3H-benzo[f]chromen-3-one (5) under refluxing conditions in ethanol using catalytic amounts of acetic acid providing good yields (76-89%). The schematic representation is shown in Scheme I.

To optimize the reaction conditions, initially the reaction of 6-methoxy-1-tetralone 1b with thiosemicarbazide 2 and 3-(2-bromoacetyl)-2H-chromen-2-one 4 was carried out in different solvents like methanol, ethanol and acetic acid at refluxing temperature. We observed that the maximum yield (75%) of the product 7b in ethanol. We also observed the yield in methanol (60%) and in acetic acid (52%).
To improve the yield of the product 7b we tried the same reaction in methanol and ethanol using catalytic amount of acetic acid and observed an improvement in the percentage of yield in ethanol (maximum yield 89%) and in methanol (maximum yield 82%). We also observed that there is no change in the yield on addition of excess acetic acid. Hence, under these optimized conditions (ethanol + catalytic amount of acetic acid) we have synthesized all the title compounds (6a-h and 7a, 7b and 8a, 8b). All the synthesized compounds were confirmed from their spectral (IR, $^1$H and $^{13}$C NMR, and mass spectroscopy) studies and elemental analyses.

Antibacterial activity

All the synthesized compounds (6a-h and 7a, 7b and 8a, 8b) were screened for their in vitro antibacterial activity against both Gram positive bacterial strains: Staphylococcus aureus (S.aureus) and Bacillus thuringiensis (B. thuringiensis) and Gram negative bacterial strains: Escherichia coli (E.coli) and Klebsiella pneumonia (K. pneumonia) with respect to Gentamicin as positive control drug.

Zone of inhibition (in mm) values for analogs (50 µg/mL) and positive control drug Gentamicin (50 µg/mL) were determined by agar disc diffusion method\textsuperscript{24}. The bacterial strains were grown and maintained on nutrient agar plates. All the compounds as well as standard were dissolved in DMSO (50 µg/mL) and transferred to each disc with the help of a micropipette. After 24 h incubation at 37°C, the resulting zone of inhibition was measured (Table I). The resulting antibacterial data revealed that all the compounds were good to moderately active towards all tested bacterial strains. Among the synthesized compounds, those having dimethoxy, and coumarin i.e. 6h and 7a, 7b, 8a and 8b have shown prominent activity against all the tested bacterial strains compared to standard drug Gentamicin. From this result it is observed that methoxy and coumarin motif enhance the antibacterial activity of corresponding compounds compared to other compounds. The remaining compounds (6a-g) have been shown to be moderately active towards tested bacterial strains.

**Experimental Section**

All the reagents and solvents were purchased from Aldrich/Merck and used as received. Melting points were determined in open capillaries using Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as homogeneity of compounds was monitored by thin layer chromatography with F\textsubscript{254} silica-gel precoated sheets using hexane/ethyl acetate 8/2 as eluent; UV light and iodine vapors were used for detection. IR spectra were recorded on a Perkin-Elmer 100S spectrometer...
utilizing KBr pellets. \(^{1}\)H and \(^{13}\)C NMR spectra were obtained at 400 MHz and 100 MHz respectively on Bruker NMR spectrometer using DMSO-\(d_6\) as solvent and TMS as internal standard. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit and the values are within \(\pm 0.4\)% of theoretical values. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

**General procedure for the synthesis of 4-substituted thiazole derivatives (6a-h and 7a,b and 8a, b)**

A mixture of substituted phenacyl bromides (3a-d)/3-(2-bromoacetyl)-2H-chromen-2-one (4)/2-(2-bromoacetyl)-3H-benzo[\(f\)]chromen-3-one (5) (1 mmol), thiosemicarbazide (2) (1 mmol) and substituted 1-tetralone (1a, 1b) (1 mmol) were taken in 10 mL of absolute ethanol with catalytic amount of acetic acid and heated at refluxing temperature for 25-40 min. After completion of the reaction (by monitoring the reaction by TLC), the solid obtained was filtered in heating condition of contents, washed with excess ethanol and the products dried. The resulting products were purified by recrystallization from the ethanol to get analytically pure compounds.

**Spectral data**

4-(4-Chlorophenyl)-2-(2-(3,4-dihydronaphalen-1(2\(H\))-ylidene)hydrazinyl)thiazole, 6a: White solid. Reaction time 25 min. Yield 82%. \(m.p. 235-237^\circ C\); IR (KBr): 3223 (NH), 1606 (C=N), 689 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.85 (t, 2H, -CH\(_2\)), J = 5.6 Hz), 2.69-2.75 (m, 4H, -CH\(_2\)), 7.18-7.27 (m, 3H, Ar-H), 7.40 (s, 1H), 7.47 (d, 2H, Ar-H, J = 8.8 Hz), 7.87-7.99 (m, 3H, Ar-H), 11.24 (s, 1H, NH); ESI-MS: \(m/z\) 354 [M+H]\(^+\). Anal. Calcd for C\(_{19}\)H\(_{16}\)ClN\(_3\): S: C, 64.49; H, 4.56; N, 11.87. Found: C, 64.58; H, 4.48; N, 11.73.

4-(4-Bromophenyl)-2-(2-(3,4-dihydronaphalen-1(2\(H\))-ylidene)hydrazinyl)thiazole, 6b: White solid. Reaction time 32 min. Yield 85%. \(m.p. 245-247^\circ C\); IR (KBr): 3221 (NH), 1608 (C=N), 711 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.85-1.88 (m, 2H, -CH\(_2\)), 2.68-2.74 (m, 4H, -CH\(_2\)), 7.17-7.26 (m, 3H), 7.41 (s, 1H, Ar-H), 7.59-7.61 (m, 2H, Ar-H), 7.82 (d, 2H, Ar-H, J = 8.8 Hz), 7.98-8.00 (m, 1H, Ar-H), 11.24 (s, 1H, NH); ESI-MS: \(m/z\) 399 [M+H]\(^+\). Anal. Calcd for C\(_{19}\)H\(_{16}\)BrN\(_3\): S: C, 57.29; H, 4.05; N, 10.55. Found: C, 57.17; H, 4.14; N, 10.63.

4-(4-Nitrophenoxy)thiazole, 6c: Pale yellow solid. Reaction time 30 min. Yield 78%. \(m.p. 251-253^\circ C\); IR (KBr): 3238 (NH), 1615 (C=N), 1204 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.85-1.88 (m, 2H, -CH\(_2\)), 2.63 (t, 2H, -CH\(_2\)), J = 6.0 Hz), 2.69 (t, 2H, -CH\(_2\)), J = 6.4 Hz), 6.78 (d, 1H, Ar-H, J = 7.0 Hz), 6.85-6.89 (m, 1H, Ar-H), 7.33 (s, 2H, Ar-H), 7.46 (t, 1H, Ar-H, J = 7.0 Hz), 7.82-7.88 (m, 4H, Ar-H), 11.08 (s, 1H, NH); ESI-MS: \(m/z\) 364 [M\(^+\)]. Anal. Calcd for C\(_{19}\)H\(_{16}\)NO\(_2\): S: C, 62.62; H, 4.43; N, 15.37. Found: C, 62.74; H, 4.28; N, 15.15.

4-(4-Methoxyphenyl)-2-(2-(3,4-dihydronaphalen-1(2\(H\))-ylidene)hydrazinyl)thiazole, 6d: Brown solid. Reaction time 30 min. Yield 84%. \(m.p. 232-234^\circ C\); IR (KBr): 3238 (NH), 1615 (C=N), 1204 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 1.85-1.88 (m, 2H, -CH\(_2\)), 2.63 (t, 2H, -CH\(_2\)), J = 6.0 Hz), 2.69 (t, 2H, -CH\(_2\)), J = 6.4 Hz), 6.78 (d, 1H, Ar-H, J = 7.0 Hz), 6.85-6.89 (m, 1H, Ar-H), 7.33 (s, 2H, Ar-H), 7.46 (t, 1H, Ar-H, J = 7.0 Hz), 7.82-7.88 (m, 4H, Ar-H), 11.08 (s, 1H, NH); ESI-MS: \(m/z\) 364 [M\(^+\)]. Anal. Calcd for C\(_{19}\)H\(_{16}\)NO\(_2\): S: C, 62.62; H, 4.43; N, 15.37. Found: C, 62.74; H, 4.28; N, 15.15.

Table I — Antibacterial activity of 4-substituted thiazole Schiff base derivatives (6a-h and 7a, 7b and 8a, b). Zone of inhibition (ZOI) values of the compounds at 50 \(\mu\)g/mL and positive control drug Gentamicin at 50 \(\mu\)g/mL.

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<td>Gentamicin</td>
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Gentamicin 20 22 15 18
4-(4-Bromophenyl)-2-(2-(6-methoxy-3,4-dihydronapthalen-1(2H)-ylidene)hydrazinyl)thiazole, 6f: White solid. Reaction time 31 min. Yield 87%. m.p. 241-243°C; IR (KBr): 3233 (NH), 1613 (C=N), 1587, 1577. Anal. Calcd for C_{29}H_{23}BrN_{3}O_{2}: C, 62.57; H, 4.73; N, 10.95. Found: C, 62.64; H, 4.69; N, 11.03.

2-(2-(6-Methoxy-3,4-dihydronapthalen-1(2H)-ylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole, 6g: Yellow solid. Reaction time 28 min. Yield 88%. m.p. 251-253°C; IR (KBr): 1604 (C=O), 1581, 1522. Anal. Calcd for C_{23}H_{18}BrN_{3}O_{2}: C, 68.16; H, 4.42; N, 11.02.

3-(2-(2-(6-Methoxy-3,4-dihydronapthalen-1(2H)-ylidene)hydrazinyl)thiazol-4-yl)-2H-chromen-2-one, 7a: Yellow solid. Reaction time 37 min. Yield 89%. m.p. 258-260°C; IR (KBr): 3237 (NH), 1718 (C=O), 1604 (C=O). Anal. Calcd for C_{20}H_{14}BrN_{3}O_{2}: C, 62.64; H, 4.69; N, 11.03. Found: C, 62.64; H, 4.69; N, 11.03.

3-(2-(2-(3,4-Dihydronapthalen-1(2H)-ylidene)hydrazinyl)chromen-3-one, 7b: Yellow solid. Reaction time 32 min. Yield 89%. m.p. 241-243°C; IR (KBr): 3233 (NH), 1718 (C=O), 1604 (C=O). Anal. Calcd for C_{20}H_{14}BrN_{3}O_{2}: C, 62.64; H, 4.69; N, 11.03. Found: C, 62.64; H, 4.69; N, 11.03.
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126.0, 128.4, 128.6, 129.0, 130.0, 132.8, 133.5, 141.1, 151.8, 158.6, 159.6, 169.4; ESI-MS: m/z 468 [M+H]+.


Conclusion

In conclusion, a series of 4-substituted thiazole Schiff base derivatives have been synthesized via one pot multi component reaction under conventional method and their antibacterial activity evaluated. Among all the compounds, dimethoxy and coumarin incorporated derivatives 6h, 7a, 7b, 8a and 8b have shown marked antibacterial activity. This investigation can be useful for further development of potent antibacterial agents.

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References