

## Synthesis of Some Novel Thiazolyl - Azetidinone Hybrids

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**ABSTRACT.** A new series of hydrazino thiazolyl-2-azetidinone **4(a-i)** derivatives were synthesized efficiently using benzylidene hydrazinyl thiazole derivatives **3(a-i)**. The precursors, benzylidene hydrazinyl thiazoles were prepared by reacting 4-fluoro phenacyl bromide with thiosemicarbazones **2(a-i)**. All the structures of the synthesized compounds were ascertained by IR, NMR and mass spectral analysis.

**Key words:** Azetidinone, Benzylidene hydrazinyl thiazole, 4-Fluoro phenacyl bromide, Thiosemicarbazone

### INTRODUCTION

Azetidinones, also known as  $\beta$ -lactams occupy a central place among medicinally important moieties due to their diverse and intense antibiotic properties. The  $\beta$ -lactam ring is a part of the core structure of several antibiotic families, the principal one being the well-known penicillins, cephalosporins, carbapenems and monobactams, which are, therefore also called  $\beta$ -lactam antibiotics.<sup>1</sup>

The antibiotic activity of azetidinone ring-containing compounds and also their effectiveness in cholesterol absorption, enzyme inhibitions and their applications as synthons for various biologically important compounds made them appealing targets for the chemists. 2-Azetidinone scaffold possesses a wide range of promising biological activities. These compounds found to be useful in the treatment of variety of diseases and disorders like atherosclerotic coronary artery disease, allergic and inflammatory condition, autoimmune disease, asthma, arterial thrombosis, rheumatoid arthritis, pneumonitis, retinitis, oesophagitis, colitis, osteoporosis, diabetes and cancer.<sup>2-5</sup> Future investigations of this scaffold could provide some more lead compounds to develop active drugs for various diseases.

On the other hand, thiazole and its derivatives have been molecules of interest being associated with wide spectrum biological and pharmacological activities, like antibacterial, antiprotozoal, antimalarial, anticancer, antiallergic, gene-modulating activities, antischizophrenia, antihypertension, anti-inflammation, anti-HIV infections and many more.<sup>6,7</sup>

In recent times, the novel concept of generating hybrid molecules by combining two differently active pharmacophore into single unit is becoming an effective strategy

in drug development. Prompted by this strategy of drug development, we have prepared new molecular hybrids by combining thiazoles with azetidinones to have new thiazolyl azetidinone derivatives expecting an improved pharmacological activities.

Since the development of penicillin, various compounds have been studied and variety of synthetic methods have been developed for their preparation. Staudinger's ketene imine reaction is the most common method for the synthesis of monocyclic 2-azetidinone. Numerous monocyclic  $\beta$ -lactams have been prepared by the reaction of acid chloride and imine in the presence of a tertiary amine or a diazoketone as ketene precursor.<sup>8-11</sup> A detailed review article on recent progress in the synthesis and chemistry of azetidinone has been reported.<sup>12</sup> In view of these fascinating studies and in continuation of our work on nitrogen and sulfur heterocycles, we have synthesized some novel thiazolyl-azetidinone derivatives from imines of hydrazinyl-thiazoles using chloroacetyl chloride in the presence of triethyl amine, which can be considered as a new lead for the development of potent pharmaceutical compounds.

### EXPERIMENTAL

#### Experimental Protocols

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on Shimadzu infrared spectrometer-8400s using KBr as background. NMR spectra of the samples were recorded on a Bruker NMR-400MHz using TMS as an internal standard. Mass spectral analysis is done by Agilent 6520 ESIQTOF MS spectral analyzer.

## Synthesis

**General Procedure for the synthesis of (2Z)-2-(substituted benzylidene) hydrazine carbothioamide, 2(a-i):**<sup>13</sup> Thiosemicarbazide (0.005 mol) was dissolved in 10 mL of the methanol by heating. The solution of substituted benzaldehyde **1(a-i)** in methanol was added to the same and then 3-4 drops of glacial acetic acid was added and refluxed at 80 °C for 3 hours. Mixture was cooled to room temperature and then filtered and washed with aqueous methanol and dried. The crude product was recrystallized using ethanol.

**General procedure for the synthesis of 2-[2-(4-substituted benzylidene)hydrazinyl]-4-(4-fluorophenyl)-1,3-thiazole, 3(a-i):**<sup>14</sup> Thiosemicarbazone (0.001 mol) **2(a-i)** was dissolved in absolute alcohol by warming. The solution of 4-fluoro phenacyl bromide in absolute alcohol was added to the same flask and refluxed at 80 °C for 3 hours. Stopped refluxing and allowed to stand at room temperature, then filtered under vacuum, washed with ethanol and dried. Crude products were recrystallized using absolute ethanol.

**General procedure for the synthesis of 3-chloro-4-[(4-substituted benzylidene)-1-{4-(4-fluoro-phenyl)-1,3-thiazol-2-yl} amino] azetid-2-one, 4(a-i):**<sup>15</sup> 2-[2-(4-substituted-benzylidene)hydrazinyl]-4-(4-fluoro-phenyl)-1,3-thiazole (0.1 mmol) was dissolved using 1, 4-dioxane and kept in ice bath. Chloroacetyl chloride was added drop wise, followed by 0.5 mL triethylamine. The mixture was stirred for 24 hours at room temperature. The contents were filtered and dried.

**3-Chloro-4-phenyl-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]azetid-2-one (4a):** Yield 59%, m.p. 169–171 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3328 (N-H), 3123 (Ar C-H), 2891 (C-H thiazole), 2869 (C-H), 1695 (-C=O), 1581 (C=N thiazole), 759 (-C-Cl), 708 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.12 (s, 1H, NH), 7.42 (s, 1H, C=CH), 7.28-7.60 (m, 9H, Ar-H), 5.15 (d, 1H, -CH-Cl), 4.12 (d, 1H, -N-CH); MS m/z: 373 [M<sup>+</sup>].

**3-Chloro-4-(4-chlorophenyl)-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]azetid-2-one (4b):** Yield 53%, m.p. 172–174 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3331 (N-H), 3115 (Ar C-H), 2960 (C-H), 2890 (C-H thiazole), 1696 (-C=O), 1587 (-C=N thiazole), 775 (-C-Cl), 710 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.17 (s, 1H, N-H), 7.82 (s, 1H, CH), 7.15-7.72 (m, 8H, Ar-H), 5.24 (d, 1H, -CH-Cl), 4.10 (d, 1H, -N-CH); MS m/z: 408 [M<sup>+</sup>].

**3-Chloro-4-(2,4-dichlorophenyl)-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]azetid-2-one (4c):** Yield 51%, m.p. 176–178 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3324 (N-H),

3008 (Ar C-H), 2962 (C-H), 2881 (C-H thiazole), 1708 (-C=O), 1591 (C=N thiazole), 766 (-C-Cl), 715 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.68 (s, 1H, N-H), 7.88 (s, 1H, CH), 7.20-7.41 (m, 7H, Ar-H), 5.16 (d, 1H, CH-Cl), 4.12 (d, 1H, N-CH); MS m/z: 442 [M<sup>+</sup>].

**3-Chloro-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]-4-(4-hydroxyphenyl)azetid-2-one (4d):** Yield 48%, m.p. 162–164 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3545 (O-H), 3353 (N-H), 3105 (Ar C-H), 2960 (C-H), 2896 (C-H thiazole), 1701 (-C=O), 1591 (C=N), 767 (-C-Cl), 713 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 10.56 (s, 1H, N-H), 7.86 (s, 1H, CH), 7.25-7.63 (m, 8H, Ar-H), 5.40 (s, 1H, -OH), 5.12 (d, 1H, -CH-Cl), 4.10 (d, 1H, -N-CH); MS m/z: 389 [M<sup>+</sup>].

**3-Chloro-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]-4-(2-hydroxyphenyl)azetid-2-one (4e):** Yield 45%, m.p. 158–160 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3546 (O-H), 3336 (N-H), 3008 (Ar C-H), 2957 (C-H), 2876 (C-H thiazole), 1699 (-C=O), 1596 (C=N), 782 (-C-Cl), 676 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 10.64 (s, 1H, NH), 7.86 (s, 1H, CH), 7.18-7.37 (m, 8H, Ar-H), 5.25 (s, 1H, OH), 5.14 (d, 1H, -CH-Cl), 4.17 (d, 1H, -N-CH); MS m/z: 389 [M<sup>+</sup>].

**3-Chloro-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]-4-(4-methylphenyl)azetid-2-one (4f):** Yield 62%, m.p. 167–169 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3374 (N-H), 3122 (Ar C-H), 2975 (C-H), 2888 (C-H thiazole), 1689 (-C=O), 702 (C-S-C), 755 (-C-Cl); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.14 (s, 1H, NH), 7.98 (s, 1H, CH), 7.30-7.68 (m, 8H, Ar-H), 5.18 (d, 1H, -CH-Cl), 4.11 (d, 1H, -N-CH), 1.56 (s, 3H, CH<sub>3</sub>); MS m/z: 387 [M<sup>+</sup>].

**3-Chloro-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]-4-(4-methoxyphenyl)azetid-2-one (4g):** Yield 57%, m.p. 170–172 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3090 (Ar C-H), 2955 (C-H), 2894 (C-H thiazole), 1685 (-C=O), 760 (-C-Cl), 669 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 10.18 (s, 1H, NH), 7.92 (s, 1H, CH), 7.18-7.58 (m, 8H, Ar-H), 5.08 (d, 1H, -CH-Cl), 4.08 (d, 1H, -N-CH), 3.68 (s, 3H, O-CH<sub>3</sub>), 2.45 (s, 6H, CH<sub>3</sub>); MS m/z: 403 [M<sup>+</sup>].

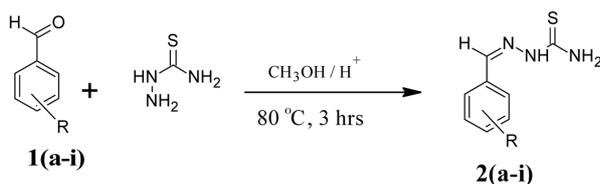
**3-Chloro-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]-4-(4-nitrophenyl)azetid-2-one (4h):** Yield 49%, m.p. 165–167 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3354 (N-H), 3094 (Ar C-H), 2989 (C-H), 2892 (C-H thiazole), 1679 (-C=O), 762 (-C-Cl), 709 (C-S-C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.82 (s, 1H, NH), 6.75 (s, 1H, CH), 7.17-7.72 (m, 8H, Ar-H), 5.23 (d, 1H, -CH-Cl), 4.19 (d, 1H, -N-CH); MS m/z: 418 [M<sup>+</sup>].

**3-Chloro-4-(4-fluorophenyl)-1-[[4-(4-fluorophenyl)-1,3-thiazol-2-yl]amino]azetid-2-one (4i):** Yield 55%, m.p. 167–169 °C; FTIR (KBr)  $\nu$  cm<sup>-1</sup>: 3348 (N-H), 3005 (Ar C-H), 2955 (C-H), 2875 (C-H thiazole), 1738 (C=O), 675 (C-S-C), 780 (-C-Cl). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ :

10.63 (s, 1H, NH), 7.83 (s, 1H, CH), 7.18-7.34 (m, 8H, Ar-H), 5.11 (d, 1H, -CH-Cl), 4.14 (d, 1H, -N-CH); MS m/z: 391 [M<sup>+</sup>].

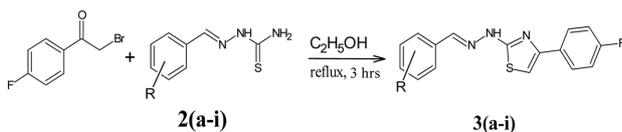
## RESULTS AND DISCUSSION

3-Chloro-4-[(4-fluorobenzylidene)-1-{4-(substituted-phenyl)-1,3-thiazol-2-yl} amino] azetidin-2-ones **4(a-i)** were synthesized in three different steps. Thiosemicarbazide on reacting with various aromatic aldehydes **1(a-i)** using methanol as solvent, yielded thiosemicarbazone derivatives **2(a-i)**. The reaction proceeded well with methanol than in ethanol as solvent. The IR spectra of the compounds **2(a-i)** displayed absorption between 1592-1604 cm<sup>-1</sup> for (C=N). The proton NMR spectra showed characteristic peak at  $\delta$  8.2 for CH=N proton and peaks at 7.79 and 11.4 for NH<sub>2</sub> and NH protons respectively. This clearly indicated the formation of thiosemicarbazones. The compounds **2(a-i)** on reaction with 4-fluoro phenacyl bromide gave compound **3(a-i)**. IR spectra of the compounds **3(a-i)** showed absorption in the region of 2879-2891 cm<sup>-1</sup> for C-H of thiazole, which confirmed the formation of thiazole ring. The <sup>1</sup>H NMR spectra of **3(a-i)** displayed a signal at  $\delta$  7.05-7.21 for C=C-H proton of thiazole. The compound **3(a-i)** on further reaction with chloroacetyl chloride in the presence of Et<sub>3</sub>N there was a formation of compounds **4(a-i)**. In the IR spectra of compounds **4(a-i)** carbonyl group of  $\beta$ -lactam ring showed characteristic absorption in the range of 1725-1746 cm<sup>-1</sup> and <sup>1</sup>H NMR spectra of compounds **4(a-i)** showed two doublet signals for (N-CH) and (CH-Cl) in the range  $\delta$  5.09-5.23 and 4.16-4.31, respectively. The doublet of C-H proton of azetidinone rings were observed



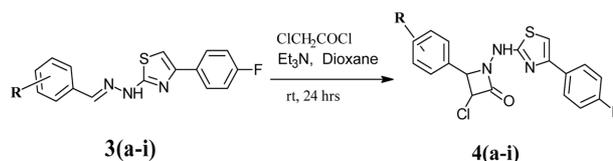
R = H, 4-Cl, 2,4-dichloro, 4-OH, 2-OH, 4-methyl, 4-methoxy, 4-nitro, 4-fluoro

**Scheme 1.** Synthesis of 2-(substituted benzylidene) hydrazine carbothioamide.



R = H, 4-Cl, 2,4-dichloro, 4-OH, 2-OH, 4-methyl, 4-methoxy, 4-nitro, 4-fluoro

**Scheme 2.** Synthesis of 2-[2-(4-substituted benzylidene) hydrazinyl]-4-(4-fluorophenyl)-1,3-thiazole.



R = H, 4-Cl, 2,4-dichloro, 4-OH, 2-OH, 4-methyl, 4-methoxy, 4-nitro, 4-fluoro

**Scheme 3.** Synthesis of 3-chloro-4-[(4-fluorobenzylidene)-1-{4-(fluorophenyl)-1,3-thiazol-2-yl} amino] azetidin-2-one.

to have coupling constant 1.3-1.8 Hz which is characteristic feature for *trans*-configuration in beta-lactam ring. Spectral characterisation of the compounds shown all the characteristic data corresponding to various functional groups and thus confirmed the formation of thiazolyl azetidinone derivatives.

## CONCLUSION

In conclusion, a new series of thiazolyl azetidinone derivatives were synthesised from multistep approach involving formation of thiosemicarbazone **2(a-i)** and then benzylidene hydrazinyl thiazole derivatives **3(a-i)** and finally the cyclisation of **3(a-i)** to have target compounds **4(a-i)**. Formation of all the compounds were confirmed with IR, NMR and mass spectral analysis. These target molecules can be considered for biological screening in order to develop active pharmaceutical compounds.

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## REFERENCES

- Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. "2-Azetidinone - A new profile of various pharmacological activities," *Eur. J. Med. Chem.* **2010**, *4*, 5541-5560.
- Wang, Y.; Zhang, H.; Huang, W.; Kong, J.; Zhou, J.; Zhang, B. "2-Azetidinone derivatives: Design, synthesis and evaluation of cholesterol absorption inhibitors," *Eur. J. Med. Chem.* **2009**, *44*, 1638-1643.
- Freddy, H. H.; Sushil, J. M. "Synthesis of some azetidin-2-ones and thiazolidin-4-ones as potential antimicrobial agents," *Ind. J. Het. Chem.* **2004**, *13*, 197-200.
- Rawat, J. M.; Srivastava, S. D. "Synthesis and biological activity of some new phenothiazino-Thia-diazoles and their Azetidinones," *Ind. J. Chem.* **1998**, *37B*, 91-94.
- Rouf, A.; Tanyeli, C. "Bioactive Thiazole and benzothiazole derivatives," *Eur. J. Med. Chem.*, doi: 10.1016/j.ejmech.2014.10.058, 2014.
- Bhat, I. K.; Chaitanya, S. K.; Satyanarayana, P. D.; Kalluraya, B. "The synthesis and antimicrobial study of some azetidinone

- derivative with some p-anisidine moiety," *J. Serb. Chem. Soc.* **2007**, *72*, 437–442.
7. Rouf, A.; Tanyeli, C. "Bioactive thiazole and benzothiazole derivatives bioactive thiazole and benzothiazole derivatives," *Eur. J. Med. Chem.* **2015**, *97*, 911–927.
  8. Kumar, M. M. J. V.; Nagaraja, T. S.; Shameer, H.; Jayachandran, E.; Sreenivasa, G. M. "N-Substituted-3-chloro-2-azetidinones: Synthesis and characterization of new novel anti-inflammatory agents," *J. Pharm. Sci. Res.* **2009**, *1*, 83–92.
  9. Pawar, P. Y.; Kalure, S. U.; Kulkarni, R. B. "Synthesis and pharmacological screening of some new azetidinone derivatives," *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 160–168.
  10. Brandi, A.; Cicchi, S.; Cordero, F. M. "Novel syntheses of azetidines and azetidinones," *Chem. Rev.* **2008**, *108*, 3988–4035.
  11. Pandey, V. K.; Gupta, V. D.; Upadhyay, M.; Singh, V. K.; Tandon, M. "Synthesis, characterization and biological activity of 1,3,4-substituted 2-azetidinones," *Ind. J. Chem.* **2005**, *44B*, 158–162.
  12. Singh, G. S. "Recent progress in the synthesis and chemistry of azetidinones," *Tetrahedron*, **2003**, *59*, 7631–7649.
  13. de Oliveira, R. B.; de Souza-Fagundes, E. M.; Soares, R. P. P.; Andrade, A. A.; Krettli, A. U.; Zani, C. L. "Synthesis and antimalarial activity of semicarbazone and thiosemicarbazone derivatives," *Eur. J. Med. Chem.* **2008**, *43*, 1983–1988.
  14. Pieroni, M.; Wan, B.; Cho, S.; Franzblau, S. G.; Costantino, G. "Design, synthesis and investigation on the structure activity relationships of N-substituted 2-aminothiazole derivatives as antitubercular agents," *Eur. J. Med. Chem.* **2014**, *72*, 26–34.
  15. Sharma, R.; Samadhiya, P.; Srivastava, S. D.; Srivastava, S. K. "Synthesis and pharmaceutical importance of 2-azetidinone derivatives of phenothiazine," *J. Chem. Sci.* **2012**, *124*, 633–637.
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