Synthesis, characterization and biological screening of some novel tetrahydroquinazoline derivatives

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Synthesis of a series of novel 4-aryl-5,5-dimethyl-7-(2′-piperidin-1′-yl-ethyl)-2-hydroxy-3,4,5,6-tetrahydroquinazolines 2a-i has been efficiently accomplished by condensation of 5,5,7-trimethyl-4-aryl-3,4,5,6-tetrahydroquinazolin-2-ols 1a-i with paraformaldehyde and piperidine in the presence of conc. HCl. All the synthesized compounds have been characterized by elemental analyses, IR, 1H NMR and mass spectroscopic investigation. All the compounds 2a-i have been evaluated for their antimicrobial and antitubercular activity.

Keywords: Tetrahydroquinazolines, antimicrobial activity, antitubercular activity

From a theoretical perspective quinazolines are undoubtedly of interest for study as they are multi-purpose heterocyclic systems with multiple reactive centers. Among them are found highly effective agricultural compounds, such as fungicides, bactericides, defoliants and plant growth stimulants. According to recent data, quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity, and many substituted quinazoline derivatives have recently earned great interest in chemotherapy as antitumor drugs. Varied biological activities have been attributed to quinazoline compounds, including analgesic, anti-inflammatory, antipyretic, antimicrobial, anticonvulsant, fungicidal, antidepressant and other central nervous system affecting activities.

In search of bioactive molecules and in continuation of our previous work in developing synthesis of polyfunctionally substituted heterocyclic compounds, we report an efficient synthesis of some novel 4-aryl-5,5-dimethyl-7-(2′-piperidin-1′-yl-ethyl)-2-hydroxy-3,4,5,6-tetrahydroquinazolines 2a-i (Table I). All the synthesized compounds 2a-i were evaluated for antimicrobial and antitubercular activity (Tables II and III).

Results and Discussion

In the present study, compounds 1a-i were synthesized in good yields by refluxing 3,5,5-trimethylcyclohex-2-en-1-one with different aromatic aldehydes and urea. The compounds 1a-i were characterized by elemental analyses and spectroscopic investigation. The IR spectrum of 1a showed characteristics bands at 2970 cm⁻¹ for -CH₃ group and 3250 cm⁻¹ for –NH group. ¹H NMR spectrum of 1a revealed singlets at δ 1.09 and 2.05 for six and three methyl protons of C-1 and C-3 respectively. Further, singlets for methine protons of C-4 and C-5 carbons at δ 4.93 and 6.01 respectively were also observed. Signal for methylene protons of C-2 at δ 2.36 as a singlet was also observed. Mass spectrum of 1a showed molecular ion peak at m/z 268.

Condensation of 1a-i with paraformaldehyde and piperidine in the presence of conc. HCl furnished the title compounds 4-aryl-5,5-dimethyl-7-(2′-piperidin-1′-yl-ethyl)-2-hydroxy-3,4,5,6-tetrahydroquinazolines 2a-i (Scheme I). The compounds 2a-i were characterized by elemental analyses and spectroscopic investigation. IR spectroscopic investigation of 2a revealed characteristic bands at 3244 and 1608 cm⁻¹ for –NH group, 3028 cm⁻¹ for aromatic C-H str. vibrations etc. ¹H NMR spectrum of 2a showed confirmatory signals at δ 3.84-3.73 and δ 4.09-3.95 as triplets for methylene protons of C-3 and C-4 respectively, also triplets at δ 2.32 and 2.89-2.85 for methylene protons of C-5 and C-6 of piperidine ring, multiplet at δ 1.46-1.42 for methylene protons of C-7 of piperidine ring were also observed. Mass spectrum of 2a showed molecular ion peak at m/z 365.

Biological screening

Antitubercular activity

Primary screening of the compounds 2a-i was conducted at 6.25 μg/mL against Mycobacterium tuberculosis Strain H37Rv (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system. All the compounds effected <90% inhibition in primary screening (i.e., MIC > 6.25 μg/mL). The compounds 2a-i were not subjected to the further evaluation due to lack of 90%
inhibition in primary screening. The results are depicted in Table III.

**Antimicrobial activity**

Products 2a-i were evaluated for their antibacterial activity against *Streptococcus pyogens* MTCC-442, *Staphylococcus aureus* subsp. *Aureus* MTCC-96, *Bacillus subtilis* MTCC-441, *Escherichia coli* MTCC-443 and antifungal activity against *Aspergillus niger* MTCC-282 and *Candida albicans* MTCC-227 using DMF as a solvent at 40 μg/mL concentration by using cup-plate method. After 24 hr of incubation at 37°C, the results are depicted in Table III.
the zones of inhibition were measured in mm. The activity was compared with some known antibiotics like ampicillin, chloramphenicol, ciprofloxacin, norfloxacin and griseofulvin at same concentration, results of which are recorded in Table II. Looking at the antimicrobial activity, four compounds (2b, 2c, 2d and 2f) demonstrated excellent antimicrobial activity compared to the standard drugs. The results led us to the SAR conclusion that presence of 2-hydroxy, 2-chloro, 4-chloro and 2-nitro substituents increase the antimicrobial activity tremendously.

**Experimental Section**

All the melting points were determined routinely in open capillaries and are uncorrected. The melting points were recorded in degree centigrade. Formation and purity of the compounds was routinely checked by TLC using silica gel-G and spots were located by iodine. ¹H NMR spectra were recorded in CDCl₃ on a Brucker DRX-300 at 300 MHz using TMS as internal standard and mass spectra were scanned on GCMS-QP2010.

**General procedure for the synthesis of 5,5,7-trimethyl-4-aryl-3,4,5,6-tetrahydroquinazolin-2-ols 1a-i**: A mixture of 3,5,5-trimethyleyclohex-2-en-1-one (0.01 moles), an aromatic aldehyde (0.01 moles) and urea (0.01 moles) was refluxed in ethanol for 10 hr. The reaction-mixture was poured into ice cold water. The product obtained was filtered, dried and recrystallized from 95% ethanol.

**General procedure for the synthesis of 4-aryl-5,5-dimethyl-7-(2′-piperidin-1′-yl-ethyl)-2-hydroxy-3,4,5,6-tetrahydroquinazolines 2a-i**: A mixture of 5,5,7-trimethyl-4-aryl-3,4,5,6-tetrahydroquinazolin-2-ols 1a-i, paraformaldehyde and piperidine in the presence of conc. HCl was refluxed in ethanol for...
Spectral data

1a: IR (KBr): 3244, 3030, 2975, 1608 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.09 (6H, s, C₁-CH₃), 2.36 (2H, s, C₂-H), 2.05 (3H, s, C₃-CH₃) 6.01 (1H, s, C₄-H), 4.93 (1H, s, C₅-H), 7.21-7.04 (5H, m, Ar-H); MS: m/z, 268 (M⁻). Anal. Calcd. for C₁₇H₂₀N₂O₂: C, 70.24; H, 5.67; N, 12.60. Found: C, 70.20; H, 5.62; N, 12.58%.

1b: IR (KBr): 3250, 3025, 2970, 1605 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.12 (6H, s, C₁-CH₃), 2.34 (2H, s, C₂-H), 2.10 (3H, s, C₃-CH₃) 6.09 (1H, s, C₄-H), 4.90 (1H, s, C₅-H), 7.33-7.02 (5H, m, Ar-H); MS: m/z, 284 (M⁺); Anal. Calcd. for C₁₉H₂₂N₂O₂: C, 71.81; H, 6.32; N, 9.85. Found: C, 71.78; H, 7.06; N, 9.88%.

1c: IR (KBr): 3245, 3020, 2970, 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.13 (6H, s, C₁-CH₃), 2.41 (2H, s, C₂-H), 2.18 (3H, s, C₃-CH₃) 6.00 (1H, s, C₄-H), 5.10 (1H, s, C₅-H), 8.01-7.29 (5H, m, Ar-H); MS: m/z, 302 (M⁺); Anal. Calcd. for C₂₁H₂₄N₂O₃: C, 75.54; H, 8.55; N, 11.50. Found: C, 75.54; H, 8.52; N, 11.46%.

1d: IR (KBr): 3240, 3020, 2970, 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.13 (6H, s, C₁-CH₃), 2.35 (2H, s, C₂-H), 2.03 (3H, s, C₃-CH₃) 6.00 (1H, s, C₄-H), 4.93 (1H, s, C₅-H), 8.05-7.35 (5H, m, Ar-H); MS: m/z, 302 (M⁺); Anal. Calcd. for C₂₁H₂₄N₂O₃: C, 75.54; H, 8.55; N, 11.50. Found: C, 75.54; H, 8.52; N, 11.46%.

1e: IR (KBr): 3245, 3025, 2970, 1605 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.16 (6H, s, C₁-CH₃), 2.38 (2H, s, C₂-H), 2.19 (3H, s, C₃-CH₃) 6.10 (1H, s, C₄-H), 4.98 (1H, s, C₅-H), 7.05-6.63 (5H, m, Ar-H); MS: m/z, 298 (M⁺); Anal. Calcd. for C₁₇H₂₂N₂O₃: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.44; H, 7.40; N, 9.36%.
Ar-H); MS: m/z, 399 (M⁺); Anal. Calcd. for C₂₃H₃₀N₃OCl: C, 69.07; H, 7.56; N, 10.51. Found: C, 69.03; H, 7.58; N, 10.46%.

2e: IR (KBr): 3240, 3029, 2943, 1610, 1580, 1515 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.09 (6H, s, C₁-CH₃), 2.38 (2H, s, C₂-H), 4.09-3.86 (2H, t, C₄-H) 3.89-3.78 (2H, t, C₅-H), 2.32 (4H, t, C₆,₆'-H), 2.94-2.82 (4H, t, C₇,₇'-H), 1.58-1.40 (2H, m, C₈-H), 5.98 (1H, s, C₉-H), 4.88 (1H, s, C₁₀-H), 7.13-6.88 (7H, m, Ar-H); MS: m/z, 395 (M⁺); Anal. Calcd. for C₂₃H₃₃N₃O₂: C, 72.88; H, 8.41; N, 10.62. Found: C, 72.79; H, 8.35; N, 10.56%.

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References