Synthesis, characterization and antimicrobial activity of new quinazolin-4(3H)-one schiff base derivatives

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ABSTRACT

As a part of systematic investigation of synthesis, characterization and biological activity of several new 2-[(5-substituted amino-1H-indol-1-yl)methyl] quinazolin-4(3H)-one derivatives (7a-h) have been synthesized by series of reactions such as modified Niementowski synthesis, condensation, reduction and derivatization of amino quinazolinone ring system into schiff bases by aromatic aldehydes. The new synthesized compounds were characterized using IR, 1H NMR and Mass spectroscopy together with elemental analysis. All the synthesized products were evaluated for their antibacterial activity against E. Coli MTCC 443, P. Aeruginosa MTCC 1688, S. Aureus MTCC 96 and S. Pyogenus MTCC 442 and antifungal activity against A. Niger MTCC 282. Most of the synthesized compounds exhibited significant anti-bacterial activities.

Keywords: 4(3H)-Quinazolinone, Schiff base, Antibacterial activity, Antifungal activity.

INTRODUCTION

4(3H)-Quinazolinone scaffold is a class of fused heterocycles that are of considerable interest because they possess diverse range of biological properties. Quinazolinone nuclei have drawn a great attention due to their wide range of chemotherapeutic activities including antiviral [1], antibacterial [2,3], antifungal [4,5], antimalarial [6], anticancer [7-9], antihypertensive [10], diuretic [11,12], inhibitors of derived growth factor receptor phosphorylation [13], anticonvulsant [14], ghrelin receptor antagonists [15], anti-inflammatory, analgesic, anti-oxidant [16,17] and COX-II inhibitors [18-20]. Thus, due to the diverse range of the pharmacological activities of quinazolinone derivatives, there has been an enormous interest in the synthesis of quinazolinone derivatives. The relevance of compounds composed from two or more heterocyclic rings for drug discovery, regardless of the target, can be best documented by the frequency with which bis-heterocyclic compounds were identified as the most potent ones [21].

On the other hand, indole is other important pharma-codynamic heterocyclic nuclei which when incorporated into different heterocyclic templates, have been reported to possess antimicrobial activity. Based on the above observations, it was of interest to synthesize a novel series of quinazolinone derivatives with structure modifications involving incorporation of the fluorinated aromatic moiety at 3rd position and an indole moiety at 2nd position of quinazolinone as a trial to obtain safer and potent anti-microbial agents.

CHEMISTRY

The desired 7-chloro-3-(4-fluorophenyl)-2-((5-(substituted amino)-1H-indol-1-yl)methyl)quinazolin-4(3H)-one derivatives were obtained by reacting 2-[(5-amino-1H-indol-1-yl)methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one 4 with various aromatic aldehydes to provides novel quinazolinone schiff base derivatives.

The synthesis of 2-chloromethyl-3-aryl-3H-quinazolin-4-one 2 was carried out using a modified Niementowski synthesis, beginning with the chloro-acetylation of 4-chloro anthranilic acid to yield the corresponding 2-(2-chloro-
Acetyl amino) benzoic acid 1. Acid 1 was then treated with trichlorophosphate (PCl₃) to convert into an acid chloride which was immediately treated with 4-fluoro aniline in situ to replace the chloro group of the acid chloride with 4-fluoro aniline. This was then refluxed in tetrahydrofuran to generate the cyclized product 2 [22-24]. Treatment of this 2-chloromethyl 4(3H)-quinazolinone 2 with 5-nitro indole in the presence of potassium carbonate provides 7-chloro-3-(4-fluorophenyl)-2-(5-nitro indol-1-yl methyl)-quinazolin-4(3H)-one 3 which upon reduction provides amino quinazolin-4(3H)-one 4. Various Schiff base derivatives were synthesized by reacting 2-[(5-amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one 4 with various aromatic aldehydes (Reaction scheme).

**EXPERIMENTAL SECTION**

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB 104 with KBr pellets. The ¹H-NMR (400 MHz) spectra were recorded on a Bruker 400 NMR spectrometer (with TMS as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. The purity of the compounds was checked by TLC on pre-coated SiO₂ gel (HF 254, 200 mesh) aluminium plates (E Merck) using ethyl acetate and hexane visualized in UV light. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallization before use.

**Reaction scheme**

Reagents and conditions: (a) THF, TEA, Chloro acetyl chloride, 2 h (b) THF, PCl₃, 65°C, 2 h (c) DMF, K₂CO₃, 25-28°C, 2 h (d) = MeOH, SnCl₂, 65°C, 4-5 h (e) Methanol, sub. aromatic aldehydes, reflux, 2-3 h.
Synthesis of 7-chloro-2-[(5-nitro-1H-indol-1-yl)methyl]quinazolin-4(3H)-one: [3]

4-Chloro-2-[(chloroacetyl) amino] benzoic acid (10.0 gm, 1.0 mole) was dissolved in dimethyl formamide (150 ml). Potassium carbonate (11.55 gm, 0.25 mole) was added and stirred for 1-2 hrs. After the completion of the reaction, reaction mass was poured into ice cooled water. Separated solid was filtered out and washed with water. The solid was dried to give 3 as a brownish solid. (10.23 gm, 82 %); MS m/z 449.5 (M+1); Calculated: C (61.55 %), H (3.11 %), N (12.47 %).

Synthesis of 7-chloro-2-(chloromethyl)-3-(4-fluorophenyl) quinazolin-4(3H)-one: [2]

3-Chloro-2-[(5-amino-1H-indol-1-yl)methyl]quinazolin-4(3H)-one: [1]

2-Amino-4-chloro benzoic acid (10.0 gm, 1.0 mole) was dissolved in 100ml of tetrahydrofuran and then triethyl amine (24.2 ml, 3.0 mole) was added to the reaction mixture. Reaction mixture was cooled to 0-5 °C and then a mixture of chloro acetyl chloride (5.14 ml, 1.0 mole) in tetrahydrofuran (10 ml) was added dropwise to the reaction mass. Reaction mass was warmed to room temperature and then stirred for 2 hrs. After the completion of reaction, sodium bicarbonate solution and diethyl ether was added to the reaction mass and stirred it for 10-15 minutes. Layers were separated and aqueous layer was acidified with dil. hydrochloric acid solution. Separated solid was extracted with ethyl acetate and then organic layer was concentrated to give 1 as an off white solid. (10.84 gm, 75 %); MS m/z 249 (M+1); Calculated: C (43.58 %), H (2.84 %), N (5.65 %), Found: C (43.54 %), H (2.81 %), N (5.62 %).

Synthesis of 7-chloro-3-(4-fluorophenyl)-2-[(5-(substituted amino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one derivatives [7a-h]

Synthesis of 7-chloro-3-(4-fluorophenyl)-2-[(5-(5-nitro-1H-indol-1-yl)methyl]quinazolin-4(3H)-one: [3]

A mixture of 2-[5-(5-nitro-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one (10.0 gm, 1.0 mole) and 4-fluoro aniline (3.89 ml, 1.0 mole) was dissolved in tetrahydrofuran (100 ml) and cooled it to 20-25 °C. Phosphorus trichloride (5.23 ml, 1.5 mole) was added to the reaction mass dropwise. Reaction mass was stirred at 60-65 °C for 2 hrs. After the completion of the reaction, reaction mass was poured into ice cooled water and then extract with ethyl acetate. Layers were separated and organic layer was washed with sat. sodium bicarbonate solution followed by water. Organic layer was concentrated and 25 ml of hexane was added. Slurry stirred for 20-30 minutes and then filtered out and washed with 10 ml cooled hexane to give 2 as a white solid. (9.11 gm, 70 %); MS m/z 324 (M+1); Elemental Analysis: Calculated: C (55.75 %), H (2.81 %), N (8.67 %), Found: C (55.72 %), H (2.80 %), N (8.64 %).

Synthesis of 7-chloro-3-(4-fluorophenyl)-2-[(5-(benzylideneamino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one [7c]:

7-Chloro-3-(4-fluorophenyl)-2-[(5-(2-fluorobenzylideneamino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one was dried to give 3 as a brownish solid. (10.23 gm, 82 %); MS m/z 449.5 (M+1); Calculated: C (61.55 %), H (3.11 %), N (12.47 %).

Synthesis of 7-chloro-2-(chloromethyl)-3-(4-fluorophenyl) quinazolin-4(3H)-one:

2-Amino-4-chloro benzoic acid (10.0 gm, 1.0 mole) was dissolved in 100ml of tetrahydrofuran and then triethyl amine (24.2 ml, 3.0 mole) was added to the reaction mixture. Reaction mixture was cooled to 0-5 °C. Aromatic aldehyde (1.0 mole) in methanol was heated to reflux for 2-3 hrs. After completion of reaction, reaction mass was cooled to 0-5 °C. Phosphorus trichloride (5.23 ml, 1.5 mole) was added and stirred for 20-30 minutes. 7-chloro-2-(chloromethyl)-3-(4-fluorophenyl) quinazolin-4(3H)-one (9.0 gm, 1 mole) was added and then reaction mass was stirred for 1-2 hrs. After the completion of reaction, reaction mass was poured into ice cooled water. Separated solid was filtered out and wash with water. The solid was dried to give 2 as a brownish solid. (10.23 gm, 82 %); MS m/z 449.5 (M+1); Calculated: C (61.55 %), H (3.14 %), N (13.38 %), Found: C (61.53 %), H (3.11 %), N (13.45 %).

General procedure for synthesis of 7-chloro-3-(4-fluorophenyl)-2-[(5-(substituted amino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one derivatives [7a-h]

A mixture of 2-[5-(5-amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one (1.0 mole) & aromatic aldehyde (1.0 mole) in methanol was heated to reflux for 2-3 hrs. After completion of reaction, reaction mass was cooled to 0-5°C. Separated solid was filtered out and wash with cooled methanol. Recrystallized with methanol to give pure solid compound 7a-h.

7-Chloro-3-(4-fluorophenyl)-2-[(5-(4-methoxy benzylidene-amino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one [7a]:

Yield: 68 %; MS m/z: 537 (M+1); mp 180-182 °C; IR (KBr, cm⁻¹): 3151, 3029, 2977, 2905, 2788, 2744, 1648, 860, 780; ¹H NMR (CDCl₃, δ ppm): 3.9 (s, 3H, -OCH₃), 5.11 (s, 2H, -CH₂), 8.45 (1H, CH=N); Calculated: C (71.06 %), H (3.85 %), N (13.38 %), Found: C (65.95 %), H (3.83 %), N (13.35 %).

7-Chloro-3-(4-fluorophenyl)-2-[(5-(5-nitro-1H-indol-1-yl)methyl]quinazolin-4(3H)-one [7b]:

Yield: 89.0 %; MS m/z: 525 (M+1); mp 206-208 °C; IR (KBr, cm⁻¹): 3319, 3184, 3149, 3097, 3020, 2983, 2947, 2839, 1652, 1315, 763; ¹H NMR (CDCl₃, δ ppm): 5.09 (s, 2H, -CH₂), 8.85 (1H, CH=N); Calculated: C (68.64 %), H (3.65 %), N (10.67 %), Found: C (68.62 %), H (3.62 %), N (10.64 %).

7-Chloro-3-(4-fluorophenyl)-2-[(5-(benzylideneamino) -1H-indol-1-yl) methyl]quinazolin-4(3H)-one [7c]:

Yield: 62.0 %; mp 210-212 °C; MS m/z: 507 (M+1); IR (KBr, cm⁻¹): 3287, 3176, 3115, 3039, 3024, 2979, 2951, 2858, 1662, 1337, 779; ¹H NMR (CDCl₃, δ ppm): 5.10 (s, 2H, -CH₂), 8.54 (1H, CH=N); Calculated: C (71.06 %), H (3.98 %), N (11.05 %), Found: C (71.03 %), H (3.95 %), N (11.02 %).
7-Chloro-3-(4-fluorophenyl)-2-((5-(4-nitro benzylideneamino) -1H-indol-1-yl)methyl)quinazolin-4(3H)-one [7d]: Yield: 65.0 %; mp 222-224 °C; MS m/z: 552 (M+1); IR (KBr, cm⁻¹): 3192, 3086, 3011, 2945, 2862, 1639, 1348, 759; ¹H NMR (CDCl₃, δ ppm): 5.13 (s, 2H, -CH₂), 8.97 (1H, CH=N); Calculated: C (65.28 %), H (3.47 %), N (12.69 %), Found: C (65.26 %), H (3.44 %), N (12.67 %).

7-Chloro-3-(4-fluorophenyl)-2-((5-(4-cyano benzylideneamino) -1H-indol-1-yl)methyl)quinazolin-4(3H)-one [7e]: Yield: 64.0 %; mp 245-247 °C; MS m/z: 532 (M+1); IR (KBr, cm⁻¹): 3254, 3186, 3066, 2974, 2962, 2858, 1647, 1341, 783; ¹H NMR (CDCl₃, δ ppm): 5.14 (s, 2H, -CH₂), 8.81 (1H, CH=N); Calculated: C (69.99 %), H (3.60 %), N (13.17 %), Found: C (69.96 %), H (3.58 %), N (13.14 %).

7-Chloro-3-(4-fluorophenyl)-2-{5-[(2-naphthalen-1-y lmethylene)amino]-indol-1-yl}quinazolin-4(3H)-one [7f]: Yield: 70.0 %; mp 214-216 °C; MS m/z: 558 (M+1); IR (KBr, cm⁻¹): 3346, 3157, 3112, 3094, 3037, 2954, 2851, 1661, 1328, 749; ¹H NMR (CDCl₃, δ ppm): 5.11 (s, 2H, -CH₂), 8.59 (1H, CH=N); Calculated: C (73.31 %), H (3.98 %), N (10.67 %), Found: C (73.29 %), H (3.96 %), N (10.64 %).

7-Chloro-3-(4-fluorophenyl)-2-((5-(2-nitro benzylideneamino) -1H-indol-1-yl)methyl)quinazolin-4(3H)-one [7g]: Yield: 66.0 %; mp 212-214 °C; MS m/z: 552 (M+1); IR (KBr, cm⁻¹): 3337, 3176, 3142, 3075, 3031, 2992, 2934, 2857, 1643, 1349, 785; ¹H NMR (CDCl₃, δ ppm): 5.08 (s, 2H, -CH₂), 9.26 (1H, CH=N); Calculated: C (65.28 %), H (3.47 %), N (12.69 %), Found: C (65.26 %), H (3.44 %), N (12.67 %).

7-Chloro-3-(4-fluorophenyl)-2-((5-(4-fluoro benzylideneamino) -1H-indol-1-yl)methyl)quinazolin-4(3H)-one [7h]: Yield: 78.0 %; mp 186-188 °C; MS m/z: 525 (M+1); IR (KBr, cm⁻¹): 3287, 3124, 3093, 3058, 2962, 2912, 2847, 1643, 1349, 764; ¹H NMR (CDCl₃, δ ppm): 5.15 (s, 2H, -CH₂), 8.79 (1H, CH=N); Calculated: C (68.64 %), H (3.65 %), N (10.67 %), Found: C (68.61 %), H (3.63 %), N (10.64 %).

The physical data are recorded in Table 1.

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<th>Yield %</th>
<th>% Composition</th>
<th>Calc./Found</th>
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Table 1 Physical constants of 2-[(5-substituted amino-1H-indol-1-yl)methyl]-7-chloro-3-(4-fluorophenyl)quinazolin-4(3H)-one

The physical data are recorded in Table 1.

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<th>Comp. No.</th>
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<th>Minimal fungicidal concentration (µg/ml)</th>
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Table 2 Antibacterial and antifungal activity of the newly synthesized compounds
RESULTS AND DISCUSSION

Spectral characteristics
The structures of all the compounds 7a-h were confirmed by various spectroscopic techniques, including IR, $^1$H NMR and mass spectroscopy. The IR spectra of 7a-h showed characteristic broad absorption band at 1639-1660 cm$^{-1}$, which confirmed the formation of amide. The band at 1589-1597 cm$^{-1}$ showed the confirmation of C=N group of quinazolinone ring. Other characteristic band of all the compounds 7a-h appearing at 765-780 cm$^{-1}$ is due to the C-Cl stretching of chloro group.

The $^1$H-NMR (400 MHz) spectra were recorded on a Bruker 400 NMR spectrometer (with TMS as internal references). Singlet at $\delta = 5.09-5.15$ ppm, which can be attributed to the methylene group attached to indole nitrogen at 1-position and quinazolinone ring at 2-position. The aromatic protons were observed from 6.46 to 8.20 ppm in the $^1$H NMR spectra.

Antimicrobial activity
All the newly synthesized compounds 7a-h were screened for antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram positive bacteria (S. Aureus MTCC 96 and S. pyogenus MTCC 442) and two Gram-negative bacteria (E. Coli MTCC 443 and P. aeruginosa MTCC 1688) and fungi A. niger MTCC 282. Antimicrobial activity (antibacterial and antifungal) was performed using broth dilution method [25]. The solution of compounds at 250 $\mu$g/ml, 200 $\mu$g/ml, 125 $\mu$g/ml and 62.5 $\mu$g/ml concentrations, were compared with standard drug Ampicillin, Chloramphenicol and Ciprofloxacin. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs ampicillin and greseofulvin. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test.

The newly synthesized organic compounds were screened through two different types of screening i.e. (1) Primary Screening using 250 $\mu$g/ml conc. (2) Secondary Screening 200 $\mu$g/ml to 62.5 $\mu$g/ml conc. The compounds which were active against the microbes in primary screening were further taken for the secondary screening.

Among the compounds of 2-[(5-substituted amino-1H-indol-1-yl)methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one series (7a-h); electronegativity of substituent at the aromatic ring of the benzylidine part manipulates the magnitude of activity. Compound 7a (4-methoxy benzylidene-amino) having electron donating group rendered the compound merely active, while their replacement by nitro group such as compound 7d (4-nitro benzylideneamino) having strong electron withdrawing group enhanced the activity & showed competitive activity against E. coli. with respect to standard drug ampicillin. Compound 7g (2-nitro benzylideneamino) found equipotent activity against E. coli. with respect to standard drug ampicillin.

Compound 7d (4-nitro benzylideneamino) found most active in the series against P. aeruginosa, however it is moderately active with respect to standard drug chloramphenicol & ciprofloxacin.

All the compounds 7a-h found active against S. aureus with respect to standard drug ampicillin. Compound 7a (4-methoxy benzylidene-amino), 7b (2-fluoro benzylideneamino), 7c (benzylideneamino) & 7f (2-naphthalen-1-ylmethylen) found more active while compound 7d (5-(4-nitro benzylideneamino), 7e (4-cyano benzylideneamino), 7g (2-nitro benzylideneamino) & 7h (4-fluoro benzylideneamino) found equipotent against S. aureus with respect to standard drug ampicillin.

Compound 7b (2-fluoro benzylideneamino) showed competitive activity against S. pyogenes with respect to standard drug chloramphenicol & ciprofloxacin and found more potent than ampicillin.

For fungi, in the series 7a-h, two compounds 7a and 7d were found active at 500 $\mu$g/ml conc. against A.niger while remaining all possessed moderate activity. Antifungal activity data were summarized in Table 2.

CONCLUSION

In Conclusions, we have identified a series of compounds based on 2-[(5-amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one (4). These compounds have been prepared by conventional method in good yield. The spectral properties, antibacterial activity and antifungal activity have been evaluated. Compounds 7b (2-fluoro benzylideneamino), 7c (benzylideneamino) & 7g (2-nitro benzylideneamino) are the most active members in this study. These three quinazolinone derivatives could be considered as useful templates for future development to obtain more potent antibacterial agent(s).
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