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Synthesis, characterization and antimicrobial activity of new quinazolin-4(3*H*)-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 3^{rd} position and an indole moiety at 2^{nd} position of quinazolinone as a trial to obtain safer and potent anti-microbial agents.

CHEMISTRY

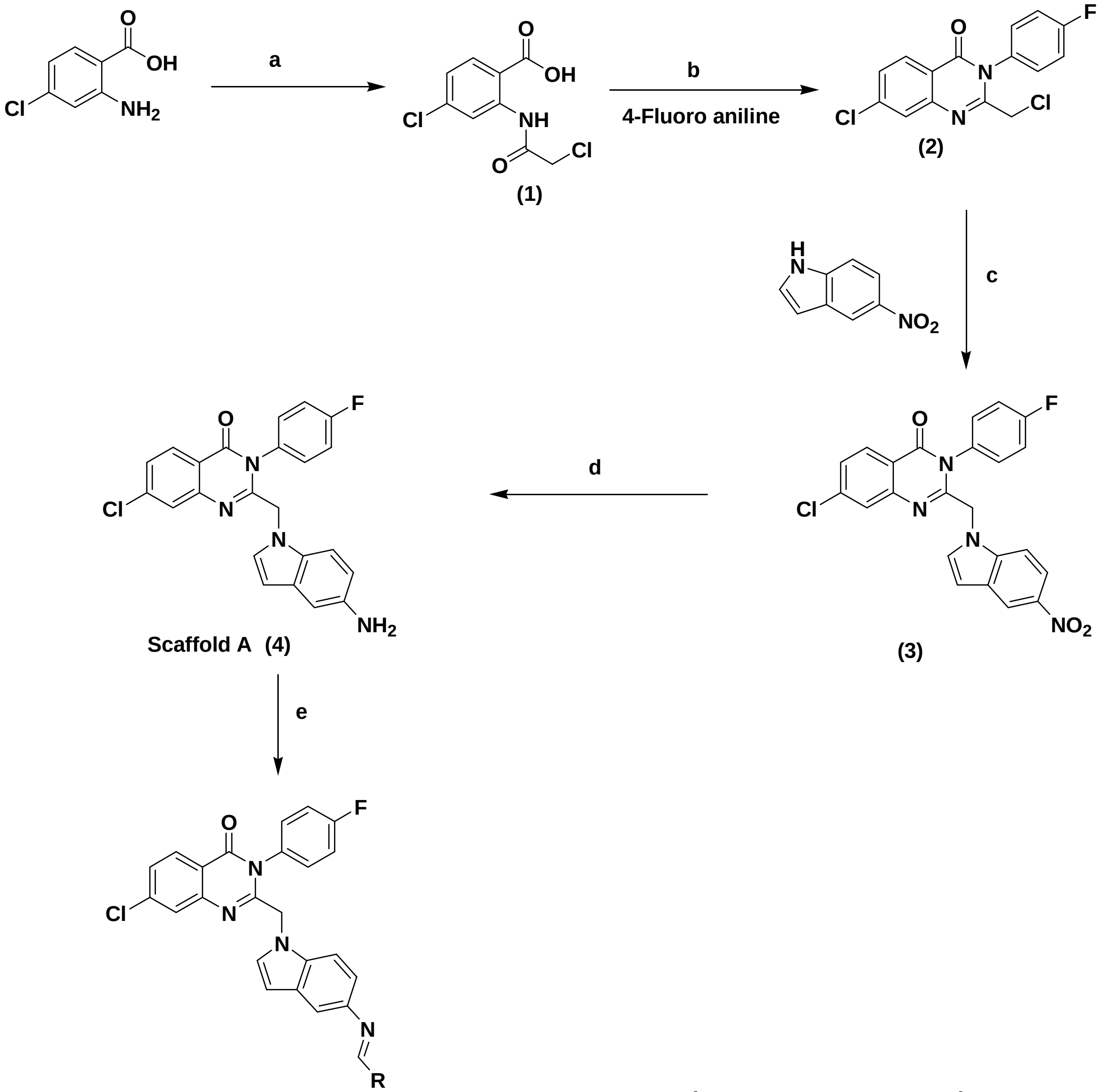
The desired 7-chloro-3-(4-fluorophenyl)-2-((5-(substituted amino) -1H-indol-1-yl) methyl)quinazolin-4(3H)-one derivatives were obtained by reacting 2-[(5-amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one 4 with various aromatic aldehydes to provides novel quinazolinone schiff 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-chloroacetyl 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 ^{1}H-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 SiO_2 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 4-chloro-2-[(chloroacetyl) amino] benzoic acid: [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 ^{o}C and then a mixture of chloro acetyl chloride (5.14 ml, 1.1 mole) in tetrahydrofuran (10 ml) was added dropwise to the reaction mass. Reaction mass was warmed to room temperature and then stirred it 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-2-(chloromethyl)-3-(4-fluorophenyl) quinazolin-4(3H)-one: [2]
4-Chloro-2-[(chloroacetyl) amino] benzoic acid (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 ^{o}C. Phosphorus trichloride (5.23 ml, 1.5 mole) was added to the reaction mass dropwise. Reaction mass was stirred at 60-65 ^{o}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 then 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 wash 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-nitro-1H-indol-1-yl)methyl]quinazolin-4(3H)-one: [3]
5-Nitro indole (4.27 gm, 0.95 mole) was dissolved in dimethyl formamide (150 ml). Potassium carbonate (11.55 gm, 3.0 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 in to ice cooled water. Seperated solid was filtered out and wash 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 (3.14 %), N (12.48 %), Found: C (61.53 %), H (3.11 %), N (12.47 %).

Synthesis of 2-[(5-amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one: [4]
7-Chloro-3-(4-fluorophenyl)-2-[(5-nitro-1H-indol-1-yl)methyl] quinazolin-4(3H)-one (10.0 gm, 1.0 mole) was dissolved in methanol. To this stannous chloride dihydrate (20.14 gm, 4.0 mole) was added and then reaction mixture was refluxed for 4-5 hrs. After the completion of reaction, reaction mass was poured in to sat. sodium bicarbonate solution and extracted with ethyl acetate. Organic layer was concentrated to give a dark brownish solid. Recrystallized with ethanol-water to give 4 as a brownish solid. (7.46 gm, 80 %); MS m/z 419.5 (M+1); Calculated: C (65.95 %), H (3.85 %), N (13.38 %), Found: C (65.93 %), H (3.83 %), N (13.35 %).

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-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 mixture was cooled to 0-5^{o} 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 ^{o}C; IR (KBr, cm^{-1}): 3151, 3029, 2977, 2905, 2788, 2744, 1648, 860, 780; ^{1}H NMR (CDCl3, δ ppm): 3.9 (s, 3H, -OCH_3), 5.11 (s, 2H, -CH_2), 8.45 (1H, CH=N); Calculated: C (69.34 %), H (4.13 %), N (10.43 %), Found: C (67.31 %), H (4.11 %), N (10.42 %).

7-Chloro-3-(4-fluorophenyl)-2-((5-(2-fluoro benzylideneamino) -1H-indol-1-yl) methyl)quinazolin-4(3H)-one [7b]: Yield: 89.0 %; MS m/z: 525 (M+1); mp 206-208 ^{o}C; IR (KBr, cm^{-1}): 3319, 3184, 3149, 3097, 3020, 2983, 2947, 2839, 1652, 1315, 763; ^{1}H NMR (CDCl3, δ ppm): 5.09 (s, 2H, -CH_2), 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 ^{o}C; MS m/z: 507 (M+1); IR (KBr, cm^{-1}): 3287, 3176, 3115, 3039, 3024, 2979, 2951, 2858, 1662, 1337, 779; ^{1}H 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 ^oC; 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 ^oC; 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-ylmethylene)amino]-indol-1-yl}quinazolin-4(3H)-one [7f]: Yield: 70.0 %; mp 214-216 ^oC; 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 (10.06 %), Found: C (73.29 %), H (3.96 %), N (10.04 %).

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 ^oC; MS m/z: 552 (M+1); IR (KBr, cm^{-1}): 3337, 3176, 3142, 3075, 3031, 2992, 2934, 2857, 1639, 1332, 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 ^oC; 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.

Table 1 Physical constants of 2-[(5-substituted amino-1H-indol-1-yl) methyl]-7-chloro-3-(4-fluorophenyl) quinazolin-4(3H)-one

Comp.	Substitution R	Molecular Formula/Weight	M.P. ^oC	Yield %	% Composition Calc./Found C	H	N
7a	4-Methoxy Ph	C31H22ClFN4O2 536.5	180-182	68	69.34 69.36	4.13 4.14	10.43 10.42
7b	2-Fluoro Ph	C30H19ClF2N4O 524.5	206-208	89	68.64 68.65	3.65 3.66	10.67 10.68
7c	Ph	C30H20ClFN4O 506.5	210-212	62	71.06 71.07	3.98 3.99	11.05 11.04
7d	4-Nitro Ph	C30H19ClFN5O3 551.5	222-224	65	65.28 65.29	3.47 3.49	12.69 12.68
7e	4-Cyano Ph	C31H19ClFN5O 531.5	245-247	64	69.99 69.98	3.60 3.61	13.17 13.18
7f	2-Naphthalene	C34H22ClFN4O 557.5	214-216	70	73.31 73.32	3.98 3.99	10.06 10.05
7g	2-Nitro Ph	C30H19ClFN5O3 551.5	212-214	66	65.28 65.26	3.47 3.49	12.69 12.71
7h	4-Fluoro Ph	C30H19ClF2N4O 524.5	186-188	78	68.64 68.65	3.65 3.65	10.67 10.66

Table 2 Antibacterial and antifungal activity of the newly synthesized compounds

Comp. No.	Minimal bactericidal concentration (µg/ml) Gram-negative *E. coli*	*P. aeruginosa*	Gram-positive *S. aureus*	*S. pyogenes*	Minimal fungicidal concentration (µg/ml) A. niger
7a	250	200	200	250	500
7b	200	250	100	62.5	1000
7c	250	200	100	250	1000
7d	125	125	250	200	500
7e	250	250	250	250	1000
7f	200	200	200	200	1000
7g	100	250	250	200	>1000
7h	250	250	250	250	1000
Ampicillin	100	--	250	100	--
Chloramphenicol	50	50	50	50	--
Ciprofloxacin	25	25	50	50	--
Nystatin	--	--	--	--	100
Greseofulvin	--	--	--	--	100

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 δ = 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 μg/ml, 200 μg/ml, 125 μg/ml and 62.5 μg/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. Muellere 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 μg/ml conc. (2) Secondary Screening 200 μg/ml to 62.5 μg/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 ampicilin. Compound 7g (2-nitro benzylideneamino) found equivipotent activity against E. coli. with respect to standard drug ampicilin.

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-ylmethylene) 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 ampicilin.

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 μg/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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