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SYNTHESIS, STRUCTURAL ELUCIDATION OF NOVEL QUINAZOLINE SUBSIDIARIES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

A progression of Novel Quinazoline subordinates 3 (a-j) have been incorporated from 2-Amino benzo/acetophenone as beginning material. The portrayal of the recently incorporated mixes was established by IR, ^{1}H NMR, ^{13}C NMR ghostly examination. The final compounds were screened for their enemy of bacterial action and antifungal movement. Against parasitic and Anti-bacterial exercises were Evaluated and saw that mixes 3i, 3j, 3e have great action.

KEYWORDS

Quinazoline subordinates, Anti-bacterial activity, Antifungal activity, 2-Amino benzo/acetophenone and Synthesis.

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INTRODUCTON

Heterocyclic chemistry is a very important branch of organic chemistry and having nearly one-third of modern publications. Originally, two thirds of organic compounds were heterocyclic compounds. An enormous number of heterocyclic compounds were known and these compounds are increasing rapidly. Accordingly the literature on the subject is very vast. Besides the vast distribution of heterocyclic compounds in natural products, they have been explored for developing pharmaceutically, agrochemical and veterinary

useful molecules. Among the Heterocyclic compounds, quinazolinone derivatives plays an important role in medicinal chemistry and useful biological activities.

Quinazoline (Figure No.1) is a compound consists of two fused six member simple aromatic rings-benzene and pyrimidine ring which is a yellow coloured compound. Medicinally it is used as antimalarial agent, prepared by Gabriel and isolated from the Chinese plant aseru. By synthesizing the compound 2-methyl-1, 3-aryl-4-quinazoline derivatives which has sedative action, the development of research on biological activity of quinazoline compounds was started. Later 48 kinds of derivatives of these derivatives with different biological actions like hypotensive, soporific, antidiabetic, sedative, antimalarial, antitussive, tranquilizing, antirheumatic, analgesic, anticonvulsant, myorelexant, antiallergic, bronchodilating, cholagogue, diuretic, cystatic etc.

Quinazoline subordinates/derivatives have a place with the Nitrogen-containing heterocyclic mixes having more significance due to their broadly and unmistakable biopharmaceutical exercises. Researchers have been resolved numerous helpful exercises of Quinazoline subordinates, including hostile to cancer[1-4], antiinflammation[5,6], antibacterial[7-10], antivirus[11], anticytotoxin[12], antispasm[13], anti tuberculosis[14], anti oxidation[15], against malarial[16], against hypertension[17], against obesity[18], antipsychotic[19], against diabetes[20], etc. Heterocyclic mixes have a focal situation in therapeutic and natural chemistry[21-23] and impressive consideration has been centered around their unions.

The quinazoline analogs are available in an assortment of organically dynamic mixes, among these are a few showcased medications like Trimetrexate glucuronate [1] (dihydrofolate reductase inhibitor), Bunazosin hydrochloride [2] and Trimazosin Hydrochloride [3] (hypotensive properties), prazosin (4), Gefitinib (5), Erlotinib (6), Alfuzosin (7), Trimetrexate (8), Vandetanib (9). [Figure No.2].

In the present Investigation, Some Substituted Novel Quinazoline mixes were incorporated and assessed for their Potential enemy of bacterial and hostile to contagious action.

MATERIAL AND METHODS

Compounds were checked for their virtue by checking TLC on silica gel G plates and spots were situated by iodine vapors. ^{1}H NMR spectra were recorded using BRUKER ADVANCE II 400 NMR Spectrometer. The NMR spectra were recorded with a 400 MHz Bruker Advance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, separately, in $CDCl_3$ arrangement with tetramethylsilane as inward standard. Proton and carbon attractive reverberation spectra (^{1}H NMR and ^{13}C NMR) were recorded utilizing tetramethylsilane (TMS) in the dissolvable of $CDCl_3$-d or DMSO-d_6 as the inner standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm. The mass spectra were recorded using JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer range RX IFT-IR System using KBr pellets. Elemental analyses of the compounds were carried out on Perkin Elmer model 2400 C H N analyzer. Every one of the mixes gave agreeable basic investigation inside ±0.4% of hypothetical qualities. All reactions were done under argon in stove dried dish sets with attractive mixing. Except if generally noticed, all materials were gotten from business providers and were utilized moving forward without any more cleaning. All solvents were reagent grade. Organic extracts were dried with anhydrous Na_2SO_4, separated through a fritted glass pipe, and focused with a rotary evaporator (20-30 Torr). Flash chromatography was performed with silica gel (200-300 mesh).

General Procedure for the preparation of 2-Phenylquinazolines:

In a 100ml round bottom flask with magnetic stirring, 2-Amino benzo/acetophenone (1.0mmol) in acetonitrile (10mL), Benzylamine (2.5m.mol), CAN (12mol %), and Di Benzoyl peroxide (10m.mol) were added and warmed to reflux under nitrogen environment at 90^{o}C until the reaction goes for completion as shown by TLC. After finishing of the reaction, the mixture was concentrated to expel acetonitrile. After dissipation of the dissolvable

under diminished weight, the unrefined buildup was removed with ethyl acetate and the consolidated natural layers were washed with salt water arrangement, dried over anhydrous Na_2SO_4, vanished to get rough item and refined by column chromatography by utilizing hexane and ethyl acetate as eluent to give the necessary compound 2-Phenylquinazoline. Every one of the items were portrayed by ^1H, ^{13}C NMR and mass spectroscopy.
Brown solid, yield 77%, m.p. 160-162^oC.

2, 4-diphenylquinazoline (3a)

IR (KBr, cm^{-1})

1611, 1560, 1529, 1331, 871, 767, 712.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ=8.11-8.17 (m, 2H), 7.81-7.90 (m, 4H), 7.53-7.56 (m, 4H) 7.37-7.43 (m, 1H), 7.01-7.09 (m, 2H) 3.89 (s, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 55.3, 113.8, 121.8, 125.7, 128.6, 128.9, 129.9, 130.1, 130.3, 130.5, 132.0, 133.9, 134.3, 137.1, 150.4, 160.1, 161.9, 167.3 ppm.

ESI-MS

313 (M+H) $^+$.

4-phenyl-2-p-tolyl quinazoline (3b)

Yellow solid, yield 79%, m.p. 168-170^oC.

IR (KBr, cm^{-1})

1614, 1561, 1533, 1335, 1074, 771, 690.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ=8.56-8.58 (m, 2H), 8.07-8.12 (m, 2H), 7.80-7.86 (m, 3H), 7.58-7.60 (m, 3H) 7.46-7.51 (m, 1H) 7.31 (d, J = 8.3 Hz, 2H), 2.46 (s, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 22.0, 121.8, 126.5, 127.2, 128.6, 128.9, 129.2, 129.8, 130.1, 133.4, 134.9, 137.6, 139.8, 150.8, 160.2, 168.0 ppm.

ESI-MS

297 (M+H) $^+$.

2-(4-methoxyphenyl)-4-phenylquinazoline (3c)

Brown solid, m.p. 159-163^oC.

IR (KBr, cm^{-1})

1625, 1551, 1531, 1337, 1075, 770, 691.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.11-8.17 (m, 2H), 7.81-7.90 (m, 4H), 7.53-7.56 (m, 4H) 7.37-7.43 (m, 1H), 7.01-7.09 (m, 2H) 3.89 (s, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 55.3, 113.8, 121.8, 125.7, 128.6, 128.9, 129.9, 130.1, 130.3, 130.5, 132.0, 133.9, 134.3, 137.1, 150.4, 160.1, 161.9, 167.3 ppm.

ESI-MS

313 (M+H) $^+$.

2-(4-chlorophenyl)-4-phenylquinazoline (3d)

Brown solid, yield 74%, m.p. 192-194^oC.

IR (KBr, cm^{-1})

1554, 1528, 1338, 853, 765, 701.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.65-8.68 (m, 2H), 8.06-8.09 (m, 2H), 7.77-7.87 (m, 3H), 7.59-7.61 (m, 3H) 7.50-7.52 (m, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 122.0, 125.7, 128.4, 128.6, 129.9, 130.1, 130.6, 130.7, 132.5, 133.2, 134.4, 137.0, 137.6, 150.4, 160.3, 167.4 ppm.

ESI-MS

317 (M+H) $^+$.

2-(4-bromophenyl)-4-phenylquinazoline (3e)

White solid, yield 73%, m.p. 142-144^oC.

IR (KBr, cm^{-1})

1552, 1518, 1328, 843, 768, 700.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.64-8.67 (m, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 8.4 Hz, 1H), 7.70-7.77 (m, 4H), 7.47-7.55 (m, 4H) ppm

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 121.4, 124.6, 126.5, 127.2, 128.5, 128.6, 129.3, 130.6, 131.7, 133.6, 134.4, 136.5, 137.9, 152.0, 160.2, 167.0 ppm.

ESI-MS

361 (M+H) $^+$;

6-chloro-2, 4-diphenylquinazoline (3f)

Yellow solid, yield 72%, m.p. 200-203^oC.

IR (KBr, cm^{-1})

1555, 1536, 1245, 843, 758.

^1H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.65-8.68 (m, 2H), 8.06-8.10 (m, 2H), 7.77-7.86 (m, 3H), 7.59-7.60 (m, 3H) 7.50-7.52 (m, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 121.8, 125.7, 128.2, 128.6, 129.7, 130.2, 130.5, 130.7, 132.5, 133.2, 134.4, 136.8, 137.6, 150.4, 160.3, 168.0 ppm.

ESI-MS

317 (M+H) $^+$.

6-chloro-2-(4-methoxyphenyl)-4-phenylquinazoline (3g)

Brown solid, yield 75%, m.p. 210-213°C.

IR (KBr, cm^{-1})

1624, 1550, 1535, 1331, 1071, 776, 690.

^{1}H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.62 (d, J = 8.6 Hz, 2H), 8.01-8.04 (m, 2H), 7.74-7.84 (m, 3H), 7.59-7.61 (m, 3H), 7.02 (d, J = 8.6 Hz, 2H), 3.88 (s, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 55.3, 113.8, 121.8, 125.7, 128.6, 128.9, 129.9, 130.1, 130.3, 130.5, 132.0, 133.9, 134.3, 137.1, 150.4, 160.1, 161.9, 167.3ppm.

ESI-MS

347 $(M+H)^+$.

6-chloro-2-(4-fluorophenyl)-4-phenylquinazoline (3h)

Yellow solid, yield 73%, m.p. 175-180°C.

IR (KBr, cm^{-1})

1553, 1526, 1336, 856, 766, 711.

^{1}H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.65-8.70 (m, 2H), 8.04-8.08 (m, 2H), 7.79-7.86 (m, 3H), 7.60-7.63 (m, 3H) 7.16-7.25 (m, 2H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 125.8, 128.4, 128.7, 130.1, 130.3, 130.9, 132.5, 134.5, 137.1, 151.0, 161.0, 167.5ppm.

ESI-MS

335$(M+H)^+$.

2-(4-fluorophenyl)-4-phenylquinazoline (3i)

Yellow solid, yield 73%, m.p. 154-156°C.

IR (KBr, cm^{-1})

1549, 1514, 1321, 846, 758, 710.

^{1}H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.67-8.70 (m, 2H), 8.07-8.10 (m, 2H), 7.76-7.85 (m, 3H), 7.60-7.63 (m, 3H) 7.52-7.54 (m, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 121.8, 124.7, 128.6, 128.9, 129.7, 130.1, 130.5, 130.7, 132.3, 133.4, 134.4, 137.2, 137.7, 150.3, 160.2, 168.0 ppm.

ESI-MS

301 $(M+H)^+$.

4-phenyl-2-(4-(trifluoromethyl) phenyl) quinazoline (3j)

Yellow solid, yield 74%, m.p. 128-130°C.

IR (KBr, cm^{-1})

1569, 1534, 1331, 826, 748, 709.

^{1}H NMR (300MHz, $CDCl_3$, TMS)

δ= 8.78 (d, J = 8.4 Hz, 2H), 8.12-8.18 (m, 2H), 7.85-7.91 (m, 3H), 7.69-7.75 (m, 3H) 7.54-7.60 (m, 3H) ppm.

^{13}C NMR (75MHz $CDCl_3$, TMS)

δ 121.9, 122.9, 124.7, 125.3, 126.0, 127.1, 127.8, 128.6, 128.9, 129.3, 130.1, 130.4, 131.7, 132.0, 132.3, 133.7, 137.2, 140.9, 151.8, 160.2, 168.0 ppm.

ESI-MS

351 $(M+H)^+$.

Biological Activity

Antibacterial studies

The antibacterial movement of compounds were tried by disc diffusion strategy against Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia and Escherichia coli (clinical seclude) bacterial strains. A standard inoculum (1-2×107 c.f.u./ml 0.5 McFarland benchmarks) was acquainted on with the outside of sterile agar plates and a sterile glass spreader was utilized for even dispersion of the inoculums. The plates estimating 6 mm in measurement was set up from Whatman no. 1 filter paper pursued by cleansing by dry warmth at 140°C for 60 minutes. The sterile plates recently absorbed a known grouping of the compounds were set in supplement agar medium. Dissolvable and development controls were kept. Amoxicillin (30µg) was utilized as positive control and the circle poured in Dimethyl sulphoxide dissolvable was utilized as negative control and the test mixes were broken down in Dimethyl sulphoxide at grouping of 100 and 50µg/mL. The plates were upset and hatched for 24 hours at 37°C. The susceptibility was surveyed based on measurement of zone of restraint against Gram-positive and Gram-negative strains of microscopic organisms. Restraint of zone of estimated and contrasted and controls. The hindrance estimations of bacterial zone are surrendered (Table No.1). The request for action was 3i>3j>3e>3h>3d >3f >3g>>3a>3b>3c.

Antifungal studies

By utilizing agar diffusion technique[34], the compounds were screened for their antifungal action against *Candida albicans* and *Aspergillus flavus* in DMSO. By dissolving peptone (1g), D-

glucose (4g) with agar (2g) in refined water (100ml) and altering p^H 5.7 Sabourauds agar media was prepared. For making the suspension of relating species, Normal saline was used. Each Petri dish was loaded up with twenty milliliters of agar media. Overabundance of suspension was tapped. The plates were dried by keeping in a hatchery at 37°C for one hour utilizing an agar punch, wells were made and every well were named. A control was additionally arranged in triplicate and kept up at 37°C for 3-4 days. The contagious action of all compounds were contrasted and Ketoconazole (standard drug). Inhibition zone were estimated and contrasted and the controls. The Inhibition values identified with fungal zone are surrendered (Table No.2).

RESULTS AND DISCUSSION

Chemistry

To an magnetically stirred 2-Amino benzo/acetophenone (1.0mmol) in acetonitrile (10mL), Benzylamine (2.5m.mol), CAN (12mol%), and Di Benzoyl peroxide (10mmol) were added and warmed to reflux under nitrogen environment at 90°C until the response goes for finishing as shown by TLC. After culmination of the response, the blend was concentrated to expel acetonitrile. After dissipation of the dissolvable under decreased weight, the unrefined buildup was extricated with ethylacetate and the consolidated natural layers were washed with saline solution arrangement, dried over anhydrous Na_2SO_4, vanished to get rough item and purged by column chromatography by utilizing hexane and ethylacetate as eluent to give the titled compound 2-Phenylquinazoline. Every one of the items were portrayed by ^1H, ^{13}C NMR and mass spectroscopy.

All compounds indicates IR, ^1H and ^{13}C NMR and mass spectra predictable with the appointed structures. ^1H NMR and IR range of mixes 6(a-j) demonstrated singlet at 2.3ppm, 3.8ppm are because of the aromatic methyl group protons and Aromatic methoxy group protons. The most characteristic IR absorption bands are at 1140cm^{-1} (C-O-C), 740cm^{-1} (C-Cl). The mass spectra of all compounds demonstrated comparable molecular ion peak with respect to molecular formula.

Anti-microbial studies

The synthesized compounds (3a-j) were screened for their in-vitro hostile to bacterial movement against *Bacillus subtilis, Staphylocouccus aureus, Klebsiella pneumonia* and *Escherichia coli* utilizing Amoxicillin as standard by disc diffusion strategy (zone of inhibition). All the tried compounds were disintegrated in dimethyl sulfoxide (DMSO) at groupings of 50 and 100µg/mL. The antibacterial screening uncovered that every one of the compounds indicates great hindrance against different tried microbial strains contrasted with the standard drug and it was discovered that mixes 3i, 3j, 8e were progressively dynamic against tried bacterial strains when contrasted with the standard. Compound 3f shows moderate antibacterial action against every single bacterial stain. The *in-vitro* antifungal activities for subsidiaries 8a-8j were controlled by agar dispersion technique. The outcomes demonstrates that, among the tried compounds 8i and 8j were dynamic against all tried fungal strains.

Table No.1: Anti-bacterial activity of compounds 8(a-j)

S.No	Synthesised Compounds	Zone of inhibition measure in mm							
		Gram positive				Gram negative			
		Bacillus subtilis		*Staphylocouccus aureus*		*Klebsiella pneumonia*		*Escherichia coli*	
		100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
1	3a	7.4	3.5	8	7	9.5	7	10.5	7.4
2	3b	7	4.6	7	4.6	8.5	6.5	9	7
3	3c	6	3	7.5	5	8	6	9.5	6
4	3d	10	8	11.1	9.5	12	11	13.5	11
5	3e	11.4	9	12.5	11	14.5	11.5	15.5	12
6	3f	9.5	7	9.5	7.5	12	10	12.5	10.5
7	3g	8.4	6.5	9.0	6.5	10.15	8	11	8
8	3h	11	9.5	11.5	8.5	12.5	12	13	11.5
9	3i	13	10.5	15	11.5	16.5	14	17	13
10	3j	12.5	10	14.5	10.5	15	13.5	16.5	12.5
11	Amoxicillin	15.6	12.6	17.4	13	18	14.6	19.6	15.6
12	Control (DMSO)	---	---	----	-----	----	-----	-----	-----

Table No.2: Anti-fungal activity of compounds 8a-j

S.No	Synthesised Compounds	Zone of inhibition measure in mm			
		Candida albicans		*Aspergillus flavus*	
		100 µg/mL	**50 µg/mL**	**100 µg/mL**	**50 µg/mL**
1	3a	8.5	5	7.5	5.5
2	3b	8	5.5	7	3.5
3	3c	6.5	4.5	7	4
4	3d	11.5	6.5	9	6
5	3e	13	11.5	10.5	8
6	3f	11	9	10	9
7	3g	9.5	7.5	8	6.5
8	3h	12.5	8	10.5	10
9	3i	17.5	12.5	16	12
10	3j	14.5	12	12.5	9.5
11	Ketoconazole	21	16	18.5	14
12	Control(dimethyl sulfoxide)	-	-	-	-

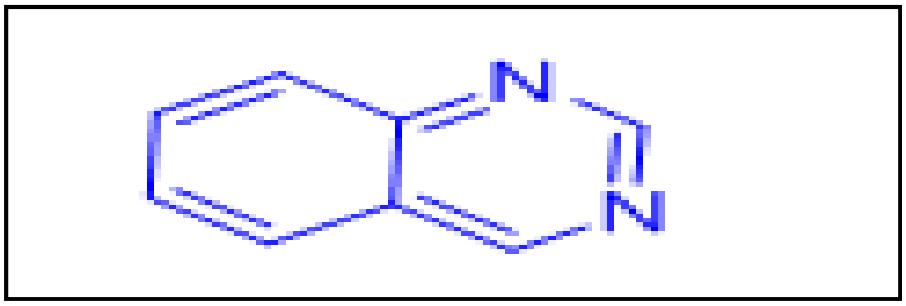


Figure No.1: Quinazoline

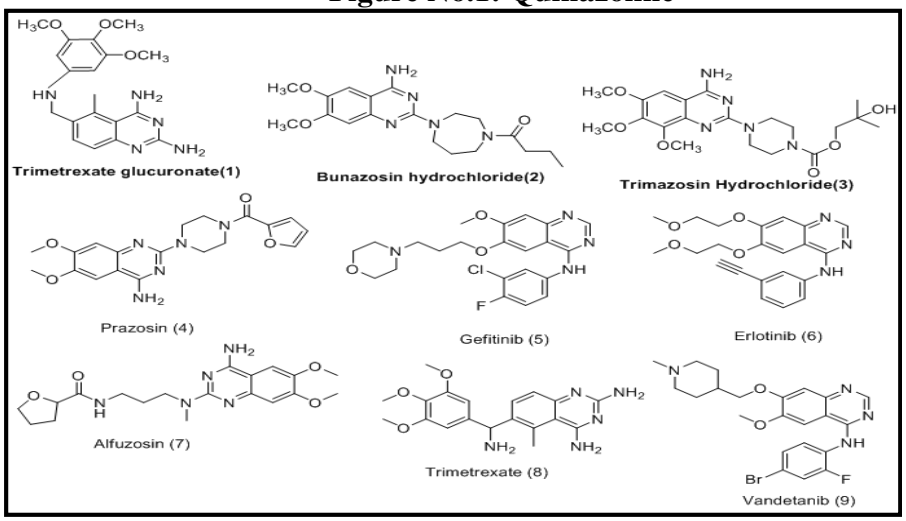
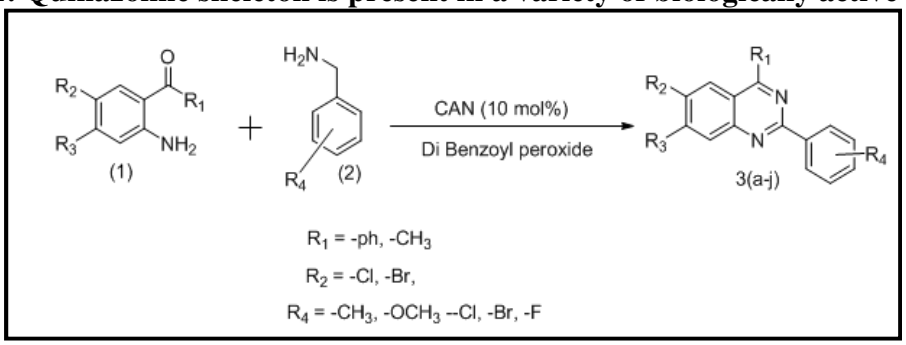
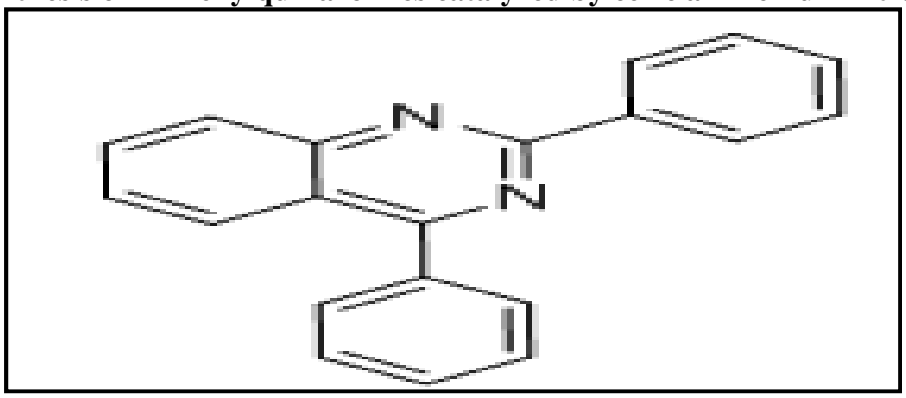


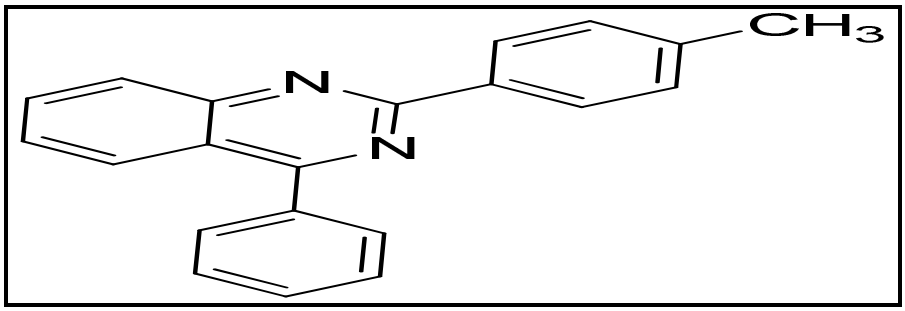
Figure No.2: Quinazoline skeleton is present in a variety of biologically active compounds



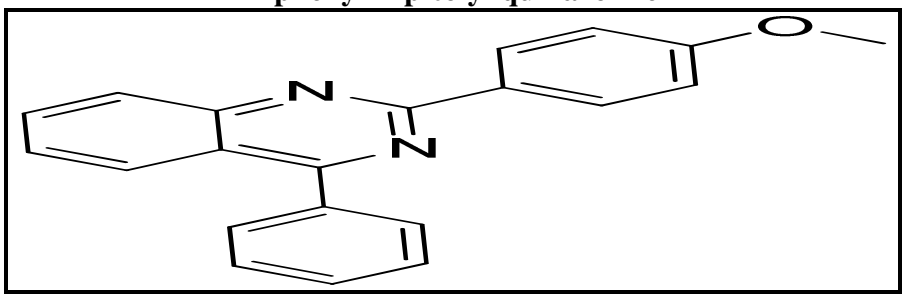
Synthesis of 2-Phenylquinazolines catalyzed by ceric ammonium nitrate



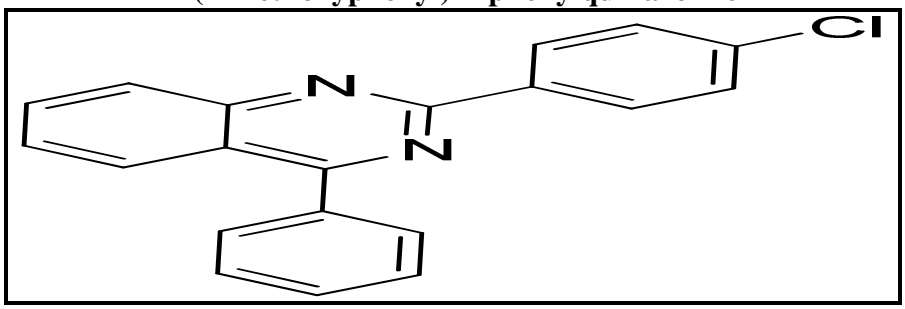
2, 4-diphenylquinazoline



4-phenyl-2-p-tolyl quinazoline



2-(4-methoxyphenyl)-4-phenylquinazoline



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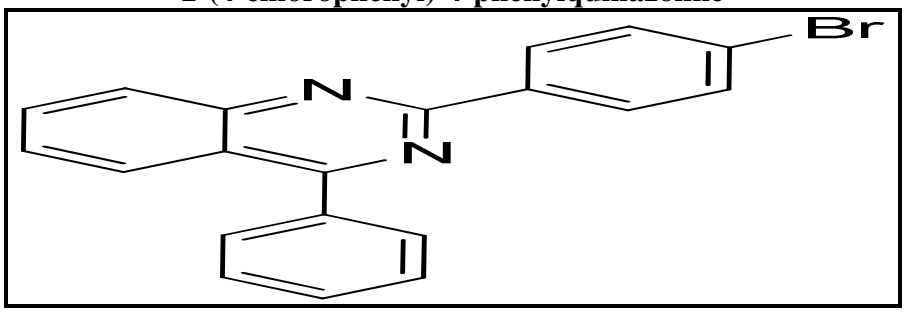

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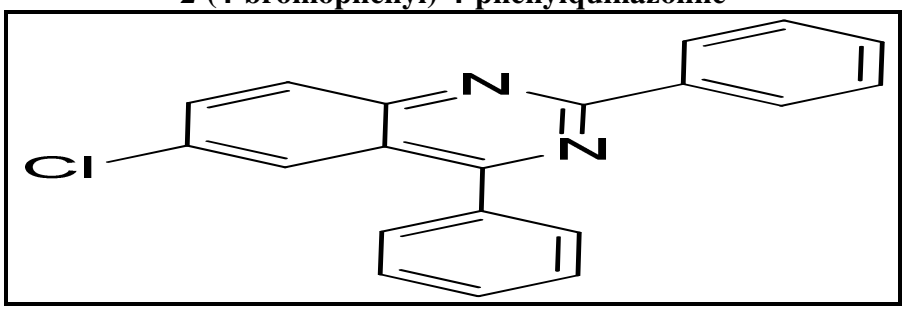
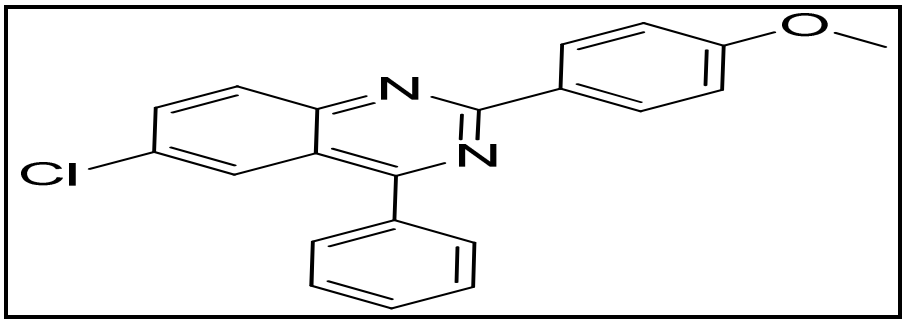
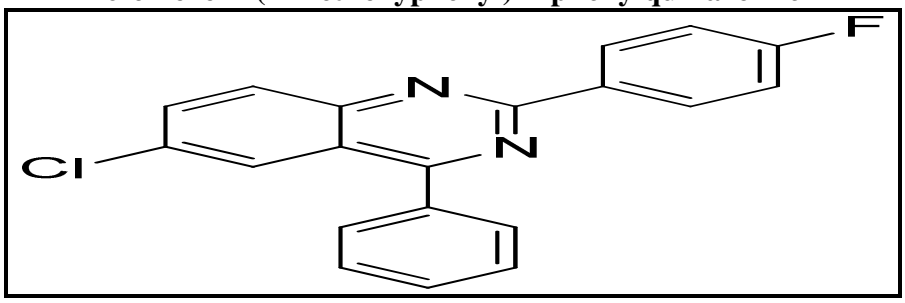


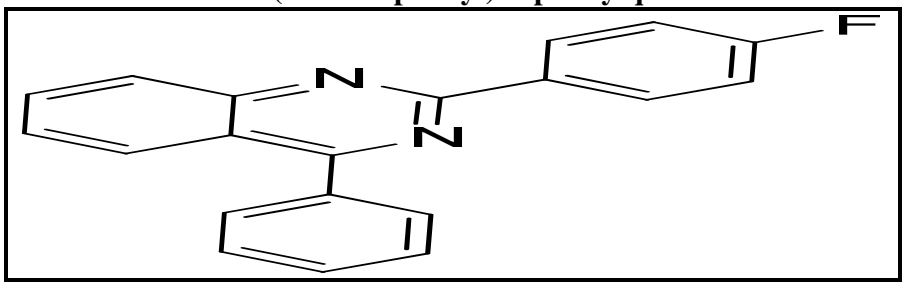
6-chloro-2, 4-diphenylquinazoline



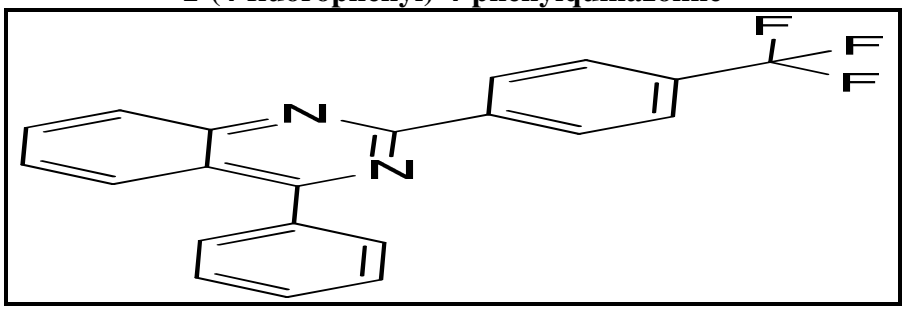
6-chloro-2-(4-methoxyphenyl)-4-phenylquinazoline



6-chloro-2-(4-fluorophenyl)-4-phenylquinazoline



2-(4-fluorophenyl)-4-phenylquinazoline



4-phenyl-2-(4-(trifluoromethyl) phenyl) quinazoline

CONCLUSION

The research concentrate reports the fruitful synthesis and against microbial activity of Quinazoline derivatives. The counter microbial action study uncovered that all the tried compounds indicated great antibacterial and antifungal activities against pathogenic strains. The structure and biological activity relationship of title compounds demonstrate that the nearness of electron withdrawing groups like - CF_3 groups appended to the Quinazoline ring is answerable for good antimicrobial action and consequently compounds 3h, 3i Exhibited increasingly powerful enemy of microbial action of all tried pathogenic strains.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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