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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF NOVEL HETEROCYCLIC COMPOUNDS

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ABSTRACT
A series of new 6-bromo-2, 3-dihydro-1, 3-dimethylbenzo (h) quinazoline-4-(1H)-one and 6-bromo-1-ethyl-2, 3-dihydro- 3-methylbenzo (h) quinazoline-4-(1H)-one and 6-bromo-2, 3-dihydro- 3-methyl-1prophylbenzo (h) quinazoline-4-(1H)-one derivatives(6a-c) were synthesized. The functional group represented in this compound was identified by FTIR analysis. In addition to this the presence of compound can also be identified from the results of Mass spectrum and ^{1}H NMR spectrum. The three components were undergone the biological study of antibacterial and antifungal activity.
Keywords: Synthesis, FTIR, Mass spectrum, ^{1}H-NMR, biological activity.

INTRODUCTION

Medicine is the most valuable assets to fight against the various disease of human health. With respect to a variety of biological activities, heterocyclic compounds occupy nearly first place among the other classes of organic compounds[1-2]. The core structure is widely used in clinically very important antibiotics like penicillin, thenamycins and quinoline-based compound. Among them fluoroquinolones are known to display anti-TB activity, mefloquine is known for its antibacterial and anti-tubercular activity.[3-4] A large number of heterocyclic compounds have been investigated for their various biological activities. Considering the above facts, this research work is aimed to design and synthesis of series of new 6-bromo-2, 3-dihydro-1, 3-dimethylbenzo (h) quinazoline-4-(1H)-one and 6-bromo-1-ethyl-2, 3-dihydro- 3-methylbenzo (h) quinazoline-4-(1H)-one and 6-bromo-2, 3-dihydro- 3-methyl-1prophylbenzo (h) quinazoline-4-(1H)-one derivatives (6a-c) compounds. Their biological activities were reported in this paper.

EXPERIMENTAL

The synthesis of above compounds involved in many steps which described below. The same was also represented schematically in Fig.-1.

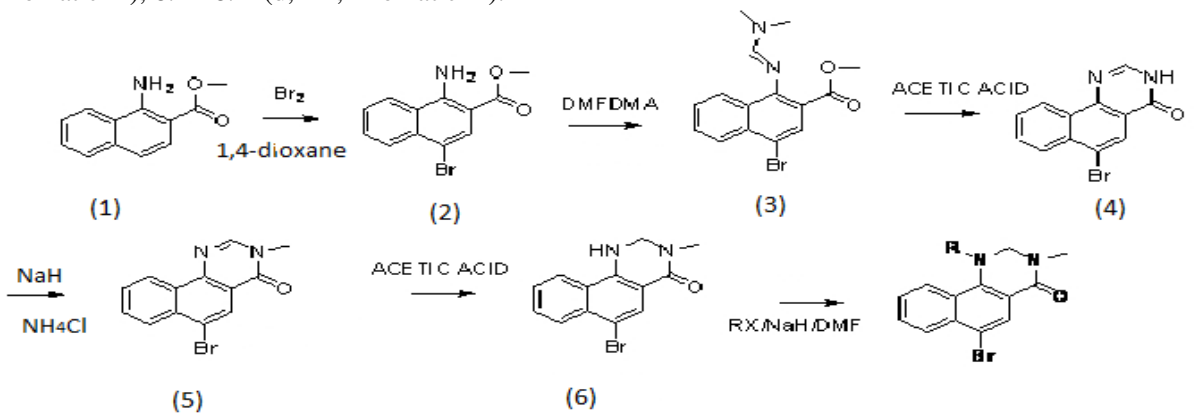
Preparation of methyl 1-amino-4-bromonaphthalene-2-carboxylate

A salt of methyl 1-aminonaphthalene-2-carboxylate (350mg) was mixed in the solution of 20ml of 1, 4-dioxane 20ml of t-butanol. It was cooled to 0°C. 2.5 ml of bromine was added slowly above solution under nitrogen atmosphere. The reaction mixture was stirred well for 3 hours using a magnetic stirrer. After completion of reaction, the obtained product was washed with water. Then it was filtered and dried to get methyl 1-amino-4-bromonaphthalene-2-carboxylate. ^{1}H NMR: (DMSO δ, ppm) δ=3.835 (s, 3H, -CH_3), 4.9(s, 2H, -NH_2), 7.59-7.63 (m, 1H, Aromatic-H), 7.45-7.78(m, 1H, Aromatic-H), 8.42-8.44(d, 1H, Aromatic-H).

Preparation of methyl 4-bromo-1-((E)-formamido) - naphthalene-2-carboxylate

220 mg of the above compound was added in 3.50 ml of N, N-dimethylformamide dimethylacetal and heated to 100°C for 5 hours. Due to chemical reaction, some residues were formed. Now it was crystallized with diethyl ether to get pure methyl 4-bromo-1-((E)-formamido) naphthalene-2-carboxylate.

^{1}H NMR: (DMSO δ, ppm) δ=3.835(s, 3H, -CH_3),7.59-7.63(m, 1H, Aromatic-H), 7.45-7.78(m, 1H, Aromatic-H), 8.42-8.44(d, 1H, Aromatic-H).



R=-CH3, -CH2CH3, -CH2CH2CH3,

Fig.-1: Schematic representation of synthesis of compounds

Preparation of 6-bromobenzo[h]quinazolin-4(3H)-one

A solution was prepared by mixing 220 mg of the above compound, 8 ml of ammonium acetate and 10ml of acetic acid and heated to 140°C for 3 hours. After completion of reaction, the product was washed with water, filtered and dried to get pure 6-bromobenzo[h] quinazolin-4(3H)-one. ^{1}H NMR: (DMSO δ, ppm) δ=12.86 (s, 3H, -NH), 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H).

Preparation of 6-bromo-3-methylbenzo[h]quinazolin-4(3H)-one

In 200mg 6-bromobenzo[h]quinazolin-4(3H)-one, 5.5 ml of DMF was added and the solution was cooled to 0°C. Then 2g of NaH was added and stirred for 30min. Now 20ml of methyl iodide was added and stirred for 1hour at RT. After completion of reaction, 20ml of saturated ammonium chloride solution was added and extracted to dichloromethane. Now it washed with water and dried; the combined organic layer was concentrated to residue to get 6-bromo-3-methylbenzo[h]quinazolin-4(3H)-one. The crude product was preceding next step with further purification. The yield: 74%, Mol .wt. (289.13). ^{1}H NMR: (DMSO δ, ppm) δ= 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H), 3.55 (s, 3H, -NCH_3).

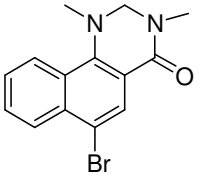
Preparation of 6-bromo-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one.

The prepared solution of 200mg 6-bromo-3-methylbenzo[h]quinazolin-4(3H)-one in 10ml acetic acid was cooled to 20°C. Small amount of zinc dust added and stirred for 2h at RT. After completion of reaction, the reaction mass was diluted with ethyl acetate and filtered through ciliate pad, wash with excess of ethyl acetate. The filtrate was concentrated and purified by column chromatography to get pure 6-bromo-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one. The yield: 75%, Mol. wt. (291.14). IR (%T, cm^{-1}): 3435.22(NH), 2947.36 (CH_3), 1597.48 (C=O), 1364.09 (CN), 755.52(C-Br).[5-7] ^{1}H NMR: (DMSO δ, ppm) δ=12.86 (s, 3H, -NH), 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H). 3.55 (s, 3H, -NCH_3).

Preparation of 6-bromo-2, 3-dihydro-1, 3-dimethylbenzo[h]quinazolin-4(1H)-one

In a beaker 6 ml of DMF was taken and 300 mg of 6-bromo-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one was mixed. The solution was cooled to 0°C. 2 gm of NaH was added and stirred for 30min then 15ml of methyl iodide was added and stirred for 1hr at RT. After completion of reaction, 20ml of saturated ammonium chloride solution was added and extracted to dichloromethane, washed with water and dried; the combined organic layer was concentrated to residue. The residue was purified by column

chromatography to get pure 6-bromo-2, 3-dihydro-1, 3-dimethylbenzo[h]quinazolin-4(1H)-one. The structure of the compound is shown in Fig.2 The yield: 65%, Mol.wt. (305.17). Melting Point: 131°C. IR (%T, cm^{-1}): 3436.62(NH), 2933.32 (CH_3), 2719.15(-NCH_3), 1594.15 (C=O), 1364.42 (CN), 652.39-766.16 (C-Br).[8-10] ^{1}H NMR: (DMSO δ, ppm) δ= 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H), 3.61 (s, 3H, -NCH_3), 3.55 (s, 3H, -NCH_3).[10-12]

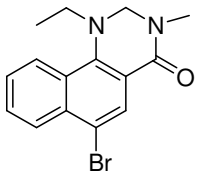


$C_{14}H_{13}BrN_2O$
Mol. Wt.: 305.17

Fig.-2: Structure of compound 6a

Preparation of 6-bromo-1-ethyl-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one

300 mg of 6-bromo-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one was mixed in 6 ml of DMF and cooled to 0°C. 2 g of NaH was added and stirred for 30min. 15ml of ethyl iodide was mixed and stirred further for 1hr at RT to get homogenous mixture. After completion of reaction, 15ml of saturated ammonium chloride solution was added and extracted to dichloromethane, washed with water and dried; the combined organic layer was concentrated to residue. The residue was purified by column chromatography to get pure 6-bromo-1-ethyl-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one. The structure of the compound is shown in Fig.3. The yield: 50%, Mol.wt. (319.20). m.p: 115°C. IR (%T, cm^{-1}): 3435.85 (NH), 2833.18. (-CH), 2719.107 (-NCH_3), 1591.91 (C=O), 1364.42 (CN), 668.56 (C-Br) [(9-11)]. ^{1}H NMR: (DMSO δ, ppm) δ= 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H), 3.55 (s, 3H, -NCH_3), 2.61-2.64 (q, 2H, -CH_2), 1.02-1.04 (t, 3H, -CH_3).

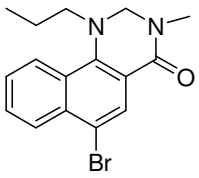


$C_{15}H_{15}BrN_2O$
Mol. Wt.: 319.2

Fig.-3: Structure of compound 6.b

Preparation of 6-bromo-2, 3-dihydro-3-methyl-1-propylbenzo[h]quinazolin-4(1H)-one

A solution of 6 ml of DMF and 300 mg of 6-bromo-2, 3-dihydro-3-methylbenzo[h]quinazolin-4(1H)-one was prepared and cooled to 0°C.In this solution, 2 gm of NaH was added and stirred for 30min. To this solution, 20ml of bromopropane was added and again stirred for 1hr at RT. After completion of reaction, 15ml of saturated ammonium chloride solution was added and extracted to dichloromethane, washed with water and dried; the combined organic layer was concentrated to residue. The residue was purified by column chromatography to get 6-bromo-2, 3-dihydro-3-methyl-1-propylbenzo[h]quinazolin-4(1H)-one. The structure of the compound is shown in Fig.-4. The yield: 50%, Mol.wt. (332.22).m.p: 105°C. IR (%T, cm-1): 3429.79 (NH), 2834.15 (-CH), 2720.64 (-NCH_3), 1593.07 (C=O), 1367.84 (CH_3), 668.56-765.16 (C-Br) (9-10). ^{1}H NMR: (DMSO δ, ppm) δ= 9.05-9.07(m, 1H, Aromatic-H), 8.48-8.49(d, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 8.31-8.34 (d, 1H, Ar-H), 8.02-8.07(m, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H), 3.55 (s, 3H, -NCH_3), 1.28 (m, 4H, -CH_2), 1.02-1.04 (t, 3H, -CH_3).



$C_{16}H_{17}BrN_2O$
Mol. Wt.: 333.22

Fig.-4: Structure of compound 6.c

Antibacterial Activities

Agar well diffusion method was employed to ascertain the antimicrobial activity of newly synthesized compounds. All the compounds were tested for their antibacterial activity against *Bacillus substilis* Staphylococcus aurous (Gram positive bacteria), *Escherichia coli*, *and Pseudomonas aeruginosa* (Gram negative bacteria) using nutrient agar medium (Table-1). Antifungal activity was carried out against *Aspergillus niger* and *Fusarium oxyporium* using potato dextrose agar medium (Table-2). DMSO was used as solvent control. The compounds were tested at a concentration of 100 µg/ml against both bacterial and fungal strains.

Preparation of Nutrient agar medium

1 lit of nutrient agar medium was prepared by mixing 2 g of beef extract, 2 g of peptone, and 10 g of agar. The ingredients were accurately weighed and dissolved in a liter of distilled water before the addition of agar. The pH of the medium was adjusted to 7.0 by adding few drops of 0.1 N NaOH/HCl. Later this medium was transferred to conical flasks and plugged with non-absorbent cotton. Medium was then sterilized by autoclaving at 15lbs pressure for 15 minutes, cooled and used for the study.

Preparation of Potato dextrose agar medium

150 g of potato was sliced and boiled with distilled water. Dextrose and agar were weighed separately. 20 g of dextrose was mixed with potato infusion. 15 g of agar was added as a solidifying agent. These constituents were mixed thoroughly and later this medium was transferred to conical flasks and plugged with non-absorbent cotton. Medium was then sterilized by autoclaving at 15lbs pressure for 25 minutes, cooled and used for the study.

Method of testing

About 15-20 ml of the sterilized media was poured onto the sterilized petri dishes and allowed to solidify. Wells of 6 mm diameter was made in the solidified media with the help of sterile borer and solutions of the test compounds were added with the help of micropipette. A sterile swab *was used to evenly distribute microbial suspension over the surface of solidified media. The plates were i*ncubated at 37°C for 24 hrs in the case of antibacterial activity and 72 hrs at 25°C for antifungal activity. The zone of inhibition was measured in mm scale.

Table-1: Antibacterial activity of synthesized compound

compound	Zone of inhibition (mm) at 100µg/ml concentration			
	Gram +Ve		Gram -Ve	
	Bacillus substilis	Staphylococcus aurous	Escherichia coli	Pseudomonas aeruginosa
6	10	09	09	-
6a	16	17	13	13
6b	18	16	16	17
6c	12	-	12	09

Antimicrobial studie

All the synthesized compounds were screened for antimicrobial activity by agar well diffusion method. The results showed that among the tested compounds 6a, 6b exhibited good activity against both gram positive and gram negative bacteria. Compound (6) is less active against Staphylococcus aurous and

Escherichia coli. Compound 6 and 6c showed inactive against *Pseudomonas aeruginosa and* Staphylococcus aurous. The compounds 6, 6b are well active against *Aspergillus Niger* and *Fusarium oxyporium*. Compound 6c do not exhibited antifungal activity. Compound 6a showed least activity towards *Aspergillus Niger* and Staphylococcus aurous and remaining compounds showed moderate activity.

Table-2: Antifungal activity of synthesized compounds

compound	Zone of inhibition (mm) at 100µg/ml concentration	
	Fusarium oxyporium	*Aspergillus niger*
6	14	14
6a	10	11
6b	14	16
6c	-	13

CONCLUSION

In this study a series of novel heterocyclic compounds containing quinazoline derivatives were synthesized.The presence of functional groups were identified with the help of FTIR and 1HNMR spectral analysis. The molecular weights of the synthesized compounds were estimated by Mass Spectrum. Melting points of these compounds were found and reported. These compounds were also undergone for antimicrobial activity. The synthesized series showed excellent to good activity against Gram-negative micro-organisms (P. aeruginosa and E. coli) and the least activity against Gram-positive bacteria (S. aureus and B. substilis). All compounds of the series exhibited moderate to less antifungal activity against *Aspergillus niger* and *Fusarium oxyporium*. The screening results revealed that most of the compounds were found to exhibit significant antimicrobial activity.

REFERENCES

1. M.L. Watt *et. a1*,*The Journal of Pharmacology and Experimental Therapeutics*, **338(3)**, 622(2011).
2. Samy M. Ibrahim, Abo-Kul M., Moustafa K. Soltan, Waleed Barkat and Ahmed S. Helal., *Med Chem.* , **4(2)**, 351 (2014)
3. Palani Venkatesh, Vijay Shankar Tiwari, *Arabian Journal of Chem.,* September 2011. doi:10.1016/j.arabjc.2011.09.004
4. Sunil Kumar, Hemlata Kaur, Indu Sharma,*World Journal of Chemistry*, **4 (2)**, 195(2009).
5. Nagaraj, Chaluvaraju, M.S. Niranjan, S. Kiran , *Int. Journal of Pharmacy and Pharmaceutical Science*, **3(3)** (2011).
6. Pravinkumar N. Sable, Swastika Ganguly, Pravin D. Chaudhar , *Chinese Chemical Letters,* **25** ,1099(2014)
7. J. Hashim, Azeez and M. Kezhal, Salih , *Res. in Pharm. Biotech.*, **3** , 1(2014).
8. V. K. Singh, S. K. Singh, Lakshmi Gangwar, *International Journal of Science and Research*, **2(4)** (2013)
9. Veena Vani Kotla, Vijaya Kumari Dalavai and Venkata Rao Chunduri, *Der Pharma Chemica*, **4(5)**, 2003(2012).
10. Nidhi Patel, F. B. Bux, Lochan Vishwas Vyavahare and Arun Singh, *Der Pharmacia Letter,***5 (3)**,336(2013)
11. Y.B. Rokade and R.Z. Sayyed, *Rasayan J. Chem.,***2(4)**, 972 (2009)
12. M.E.Abd El Fattah, A.H.Soliman and H.H.Abd Allah.,, Proceedings of 14th International Electronic Conference on Synthetic Organic Chemistry Nov-2010.

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