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MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF SOME QUINAZOLINONE BASED CONDENSED HETEROCYCLES

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ABSTRACT

Solvent free synthetic approach towards greener chemistry was followed by microwave irradiation technique. Novel series of oxazole/thiazole ring fused amino quinazolinones were synthesized and characterized. Quinazolinones represent a useful template for their wide array of pharmacological properties. Microwave irradiation technique contributed to better yield of product with shorter reaction time and minimal byproducts. Anthranilic acid **(1)** was subjected to react with 4-chloro -3-nitro benzoylchloride **(2)** leading the production of 2-(4-chloro-3-nitrophenyl)- 4H-3, 1 benzoxazin- 4-one **(3)**. Subsequently **(3)** was refluxed with 80% hydrazine hydrate **(4)** using pyridine to yield 3-amino-2-(4-chloro-3-nitrophenyl) quinazolin -4(3H) one (**5).** 2-Chloro-N-(2-(4-chloro-3-nitrophenyl)-4-oxoquinazolin-3(4H)-yl)acetamide **(7)** was synthesized by stirring and refluxing **(5)** with chloroacetylchloride **(6).** The title compounds 3-[(2-substituted -1, 3 oxazole/ thiazole) amino] 2-(3-chloro-4-nitrophenyl)quinazolinone-(**9a - 9f)** were synthesized by reacting **(7)** with different urea derivatives **(8a-8f)** in presence of ethanol under microwave irradiation technique. All synthesized compounds were characterized by IR, NMR and MS spectral data.

Key words : 3-Amino quinazolinones, 4-Nitro-3-chloro benzoylchloride, Thaizole, Oxazole, Microwave irradiation technique.

INTRODUCTION

It has been estimated that about one half of all the therapeutic agents consists of heterocyclic compounds. The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature, which are known to exhibit wide array of pharmacological properties including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, antiparkinsonism, CNS depressant, anticonvulsant, antihistaminic,

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local anesthetic, antiviral and anticancer activities[1]**.** An efficient and simple method has been designed for the synthesis of various 2-heterosubstituted quinazolinones under microwave irradiation technique. The application of microwave irradiation in chemical synthesis provides shorter reaction time, improved product yield, minimization of intermediates formation and impurity, ultimately accelerating synthetic process. In the present study, the 3rd position of quinazolinone was used as the target for chemical modifications, by incorporating different hetero nuclei. The structures of the synthesized compounds were established by IR, NMR and MS spectral data.

EXPERIMENTAL

The synthetic route is shown in **Scheme 1**. 2-(4-Chloro-3-nitrophenyl)- 4H-3, 1 benzoxazin- 4-one **(3)** was prepared in good yield by stirring cold solution of 2-amino benzoic acid and 4-chloro-3-nitro benzoylchloride in pyridine[2]**.** 3-Amino-2-(4-chloro-3-nitrophenyl)quinazolin-4(3H) one **(5)** was prepared by refluxing **(3)** with 80% hydrazine hydrate using pyridine[3]. 2-Chloro-N-(2-(4-chloro-3-nitrophenyl)-4-oxoquinazolin-3(4H)-yl)acetamide **(7)** was synthesized by stirring and refluxing **(5)** with chloroacetylchloride (**6**)[4]**.** Finally compounds (**9a-9f)** were prepared by reacting **(7)** with different urea derivatives **(8a-8f)** in presence of ethanol using microwave irradiation technique[5,] Compounds **9a –9f** were prepared in a similar manner with minor modification in irradiation power, time and heating interval and are presented in Table 1.

Table 1 : Reaction conditions

Sample code	Irradiation power	Exposure time (min)	Time interval after replacing ethanol (sec)
9a	10	15	60
9b	10	17	60
9c	10	7	30
9d	10	20	60
9e	5	15	30
9f	10	15	60

Melting points were determined by the open capillary method and are presented uncorrected. IR spectra were recorded on a Shimadzu 8700 FT-IR spectrophotometer using thin film supported on KBr pellets. ^{1}H NMR experiments (solvent DMSO) were recorded

on Bruker–NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a JEOL GC Mate II Mass spectrophotometer operating as direct probe using EI technique. Purity of all compounds were checked by TLC on precoated silica gel G plates using chloroform/ methanol (8 : 2) as developing solvent system and spots were detected on exposure to UV chamber/Iodine vapors in a tightly closed chamber. A single principal spot and no secondary spot confirmed the purity of the compounds.

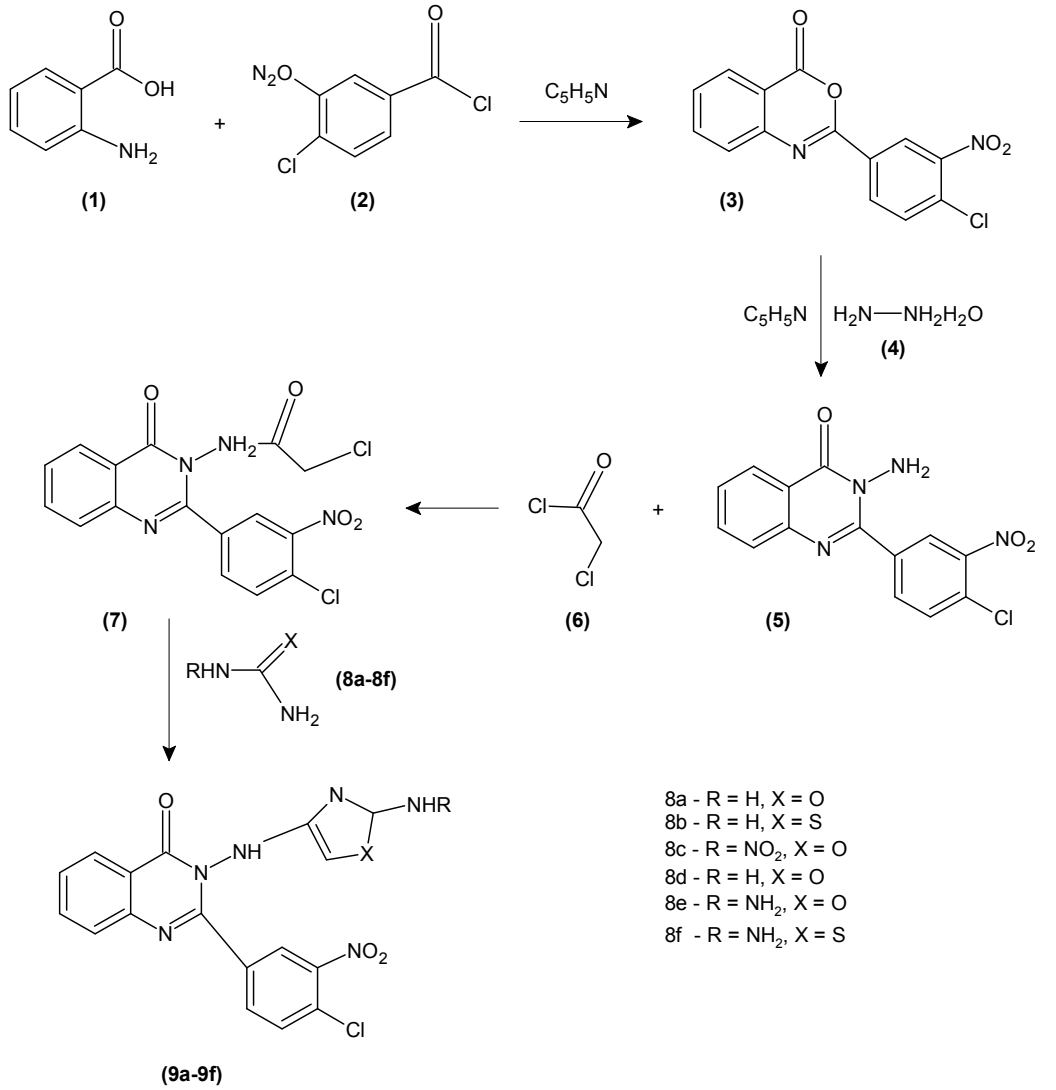

Fig. 1

3-[(2-Amino-1, 3-oxazol-4-yl) amino]-2-(3-chloro-4-nitrophenyl) quinazolin-4(3H)-one (9a)

White amorphous powder, m. p - 249°C, yield-63.00% mol. formula- $C_{17}H_{11}N_6O_4Cl$, mol. wt - 398.76, IR υ cm^{-1} (KBr) : 3026.41 (C-H str, Aromatic), 1556.61 (C-C str, Aromatic), 1688.48 (C=O str, amide), 1604.33 (C=N str,), 1022.31 (N-N str,), 1143.83, 1346.36 (C-N str,), 3346.31 (N-H str,), 1556.61 (NH_2 str,), 719.47 (C-Cls str,), 1411.94 (NO_2 str,). ^{1}H NMR δppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5 (d, NH_2), 8.3 (m, Heteror-H), MS : m/z value-398.706 $(M)^+$ ion peak..

3-[(2-Amino-1, 3-thiazol-4-yl) amino]-2-(3-chloro-4-nitrophenyl) quinazolin-4(3H)-one (9b)

Brownish powder, m. p-290°C, yield-67.75%, mol. formula- $C_{17}H_{10}N_6O_3SCl$, mol. wt-414.82564, IR υcm^{-1} (KBr) : 3070.78 (C-H str, Aromatic), 1545.03 (C- C str, Aromatic), 1612.54 (C=O str, amide), 2058.11 (C=N str,), 1020.38 (N-N str,), 1161.19, 1342.50 (C-N str,), 3342.29 (N-H str,), 1545.03 (NH_2 str,), 715.61 (C-Cl str,), 1381.08 (NO_2 str,). ^{1}H NMR δppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5 (d, NH_2), 8.3 (m, Hetero Ar-H), MS : m/z value-414.798 $(M)^+$ ion peak.

2-(3-Chloro-4-nitrophenyl)-3-{[2-(nitroamino)-1, 3-oxazol-4-yl] amino} quinazolin-4(3H)-one (9c)

Black amorphous powder, m. p-283°C, yield-68.1%, mol. formula- $C_{17}H_{10}N_7O_6Cl$, mol. wt-443.7576, IR υcm^{-1} (KBr) : 3072.71 (C-H str, Aromatic), 1500.67 (C-C str, Aromatic), 1687.83 (C=O str, amide), 1604.83 (C=N str,), 1022.31 (N-N str,), 1145.75 (C-N str,), 3497.92 (N-H str,), 1540.32 (NH_2 str,), 736.83 (C-Cl str,), 1384.94 (NO_2 str,). ^{1}H NMR δ ppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5(d, NH_2), 8.3 (m, HeteroAr-H), MS : m/z value-443.987 $(M)^+$ ion peak.

2-(3-Chloro-4-nitrophenyl)-3-{[2-(hydroxyamino)-1, 3-oxazol-4-yl] amino} quinazolin-4(3H)-one (9d)

Light brownish powder, m.= p-260°C, yield-76.61%, mol. formula-$C_{17}H_{11}N_6O_5Cl$, mol. wt-414.75, IRυcm^{-1} (KBr) : 3037.99 (C-H str, Aromatic), 1529.60 (C-C str, Aromatic), 1670.41 (C=O str, amide), 1608.69 (C=N str,), 1018.45 (N-N str,), 1195.91, 1375.29 (C-N str,), 3310.74 (N-H str,), 694.40 (C-Cl str,), 1342.50 (NO_2 str,), 3350.43 (OH str,). ^{1}HNMR δppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5 (d, NH_2), 8.3(m, HeteroAr-H), MS : m/z value- 413.987 $(M)^+$ ion peak.

2-(4-Chloro-3-nitrophenyl)-3-[(2-hydrazino-1, 3-oxazol-4-yl)amino]quinazolin-4(3H)-one(9e)

Greyish amorphous powder, m.p. - 253°C, yield-82.75%, mol. formula- $C_{17}H_{12}N_7O_4Cl$, mol. wt-413.77, IR υcm^{-1} (KBr) : 3063.06 (C-H str, Aromatic), 1568.18 (C-C str, Aromatic), 1737.92 (C=O str, amide), 1614.47 (C=N str,), 1018.45 (N-N str.), 122.61, 1247.99 (C-N str,), 3444.98 (N-H str,), 1558.18 (NH_2 str,), 788.951 (C-Cl str.), 1404.22 (NO_2 str,). ^{1}H NMR δppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5 (d, NH_2), 8.3 (m, Hetero Ar-H), MS : m/z value-413.52 $(M)^+$ ion peak.

2-(4-Chloro-3-nitrophenyl)-3-[(2-hydrazino-1, 3-thiazol-4-yl) amino] quinazolin-4(3H)-one (9f)

White amorphous powder, m..p. - 243°C, yield-81.15%, mol. formula- $C_{17}H_{12}N_7O_3SCl$, mol. wt-429.84 IR υcm^{-1} (KBr) : 3034.88 (C-H str, Aromatic), 1521.89 (C-Cstr, Aromatic), 1670.41 (C=O str, amide), 1637.62 (C=N str,), 1020.38 (N-N str,), 1122.61, 1199.46 (C-N str,), 3384.52 (N-H str,), 1612.54 (NH_2str,), 775.41 (C-Cl str,), 1334.9 (NO_2 str,). ^{1}H NMR δppm DMSO : 2.5 (s, NH), 7.5-7.7 (m, Ar-H), 3.5 (d, NH_2), 8.3 (m, Hetero Ar-H), MS : m/z value- 428.995 $(M)^+$ ion peak.

RESULTS AND DISCUSSION

It has been observed that the presence of microwave irradiation technique shortened the reaction time and minimize the byproducts formation and produce a much pure product with high yield. The reaction time for synthesis of compounds **(9a- 9f)** was shortened within 20 mins. The title compounds gave bands at 1020.25-1018.45, 1700-1600, 1360-1180, 3400-3300, 1400-1300 1650- 1560 cm^{-1} in the IR spectra due to the functional groups like N-N str, C=N str, C-N str, NH str, NH_2 str $_{and}$ NO_2 str.

The ^{1}H NMR spectral data of all the synthesized compounds were in conformity with the structure assigned. In Mass spectra of compounds, the molecular ion peaks (M^+) confirmed the molecular weights of the examined compounds. Appearance of an isotope peak (M^++2) in 1 : 3 ratio with the molecular ion peak confirmed the presence of halogen atom in the compounds.

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CONCLUSIONS

The present method of quinazolinone derivatives syntheses under microwave irradiation offers advantages of faster reaction rates and high yields. All compounds were fully characterized by spectroscopy techniques. The title compounds were found to exhibit good bioactivity against bacteria and moderate antifungal activity.

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