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SYNTHESIS AND CHARACTERISATION OF SOME TRIAZOLO QUINAZOLINE DERIVATIVES

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ABSTRACT

A series of new 3-(substituted phenyl)-8-(substituted)-9-(substituted)-[1,2,4]triazolo[4,3-c] quinazoline derivatives were synthesized by multi-component reactions of equimolar amount of 7-(substituted)-6-(substituted)-3H-quinazolin-4-one derivatives (0.1 mmole), hydrazine hydrate (0.1 mmole) and substituted aromatic aldehyde (0.1) were mixed in 25 ml ethanol. without catalyst under microwave irradiation. The compounds were synthesized in good yields (69-91%) by the microwave-assisted one-pot protocol in much shorter reaction times. All compounds were characterized by ^{1}H-, ^{13}C-NMR, IR spectral analysis. Some of the compounds were found to be effective against bacterial strains. It is an efficient, promising and green synthetic strategy to construct 3-(substituted phenyl)-8-(substituted)-9-(substituted)-[1,2,4] triazolo[4,3-c]quinazoline skeleton.

KEYWORDS: Quinazoline, Microwave-Assisted Synthesis, Multi-component reactions.

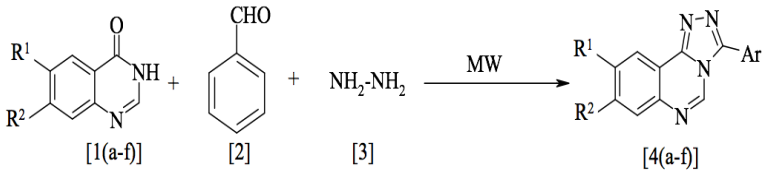
INTRODUCTION

The quinazolinone moiety is a building block for approximately150 naturally occurring alkaloids and drugs.[1] The natural quinazolinones and their synthetic analogs possess a variety of biological activities, including antimalarial[2], anticonvulsant[3], antibacterial[4], antidiabetic[5], and anticancer.[6] Thus, due to the diverse range of the pharmacological activities of quinazolinones and their derivatives, there are numerous methods available for their synthesis.[7] Among them, the main synthetic routes employ anthranilic acid (2-aminobenzoic acid), an-

thranilamide (2-aminobenzamide), isatoic anhydride, *N*-arylnitrilium salts and 3,1- benzoxazinones, as appropriate precursors.

(3*H*)-Quinazolin-4-ones

The diverse pharmacological targets of (3*H*)-quinazolin-4-ones and their derivatives explain the numerous methods available for their synthesis.[1,2] Among them, the main synthetic routes use anthranilic acid (2-aminobenzoic acid), anthranilamide (2-aminobenzamide), isatoic anhydride, *N*-arylnitrilium salts and 3,1 benzoxazinones as appropriate precursors. The most common synthetic method of the (3*H*)-quinazolin-4-one ring formation is based on the Niementowski reaction. This ring formation usually involves the reaction of anthranilic acids (or a derivative, e.g., 2- aminobenzonitrile) with formamide during extended reaction times at high temperatures.



1) R_1= H, R_2 = H
2) R_1= -CH_3, R_2 = =OCH_3
3) R1= -OCH_3, R_2 = -OCH_3
4) R_1= -OH, R_2 = -OCH_3
5) R_1= -NO_2, R_2 = -OCH_3
6) R_1= -Br, R_2 = -OCH_3

1) Ar = 2-Cl
2) Ar = 3-Cl
3) Ar = 4-Cl
4) Ar = 4-OH
5) Ar = 2,4-diCl
6) Ar = 3,4-di-OH

Fig.1

MATERIALS AND METHODS

The chemicals used in the present work are of analytical grade from Across organics ltd. The M.P.s were determined by open capillary method and were uncorrected. The products were characterized by IR, ^{1}HNMR and ^{13}C-NMR spectral studies. The IR spectra were recorded on FTIR Spectrophotometer (Perkin-Elmer) in the form of KBr pallet. 1HNMR spectra were recorded in $CDCl_3$ on a FT-NMR Spectrometer 400 MHz (Bruker) using TMS as an internal standard. The purity of compounds was checked by TLC. The crude products were recrystallised from 50:50% ethanol.

General synthetic procedure for 3-(substituted phenyl)-8,9-(substituted)-[1,2,4] triazolo[4,3-c]quinazoline

In 100ml round bottom flask, 7-(substituted)-6-(substituted)-3H-quinazolin-4-one derivatives (0.1 mmole), hydrazine hydrate (0.1 mmole) and substituted aromatic aldehyde (0.1) were mixed in 25 ml ethanol. Then the reaction mixture was irradiated with microwave at 200 power for 3 to 7.5 min to give 3-(substituted phenyl)-8-(substituted)-9-(substituted)-[1,2,4] triazolo[4,3-c]quinazoline The progress of the reaction was monitored by TLC (Pet ether: ethyl acetate 8:2). Upon completion of the reaction, the reaction mixture was cooled to room temperature, poured into crushed ice. The solid separated was filtered to give the crude products, which were further purified by recrystallization from (50:50) EtOH to give the pure derivatives.

Table-1: General characteristics and elemental analysis data of the compounds [4 (a-f)]

Comp.	Time (min.)	Yield %	MP ^{0}C	Mol. Formula (Mol.Mass)	Elemental Analysis					
					% of C		% of H		% of N	
					Found	Cal.	**Found**	Cal.	**Foun**	Cal.
4a	6.5	86	178	$C_{15}H_9ClN_4$ (280.72)	64.18	64.16	3.23	3.12	19.96	19.99
4b	3.0	73	267	$C_{17}H_{13}ClN_4O$ (324.77)	62.87	62.90	4.03	4.00	17.25	17.21
4c	7.0	91	221	$C_{17}H_{13}ClN_4O_2$ (340.77)	59.92	59.99	3.85	3.97	16.44	16.45
4d	4.5	69	187	$C_{16}H_{12}N_4O_3$ (308.30)	62.34	62.37	3.92	3.89	18.17	18.24
4e	6.0	90	233	$C_{16}H_9Cl_2N_5O_3$ (390.19)	49.25	49.18	2.32	2.33	17.95	17.86
4f	7.5	78	198	$C_{16}H_{11}BrN_4O_3$ (387.20)	49.63	49.71	2.86	2.80	14.47	14.67

Spectral Analysis

3-(2-Chloro-phenyl)-[1,2,4]triazolo[4,3-c]quinazoline (4a)

IR(KBr)ν_{max}: 1612.63 (C=N), 1597.79(>C=C<), 3136.22(Ar-CH),1228.03(N-N), 694.47 (C-Cl).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 7.21-8.05 (m, 4H, C_6H_4), 9.16 (s,1H, =CH), 7.05-8.02 (m, 4H, C_6H_4).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 116.80 (=CH), 121.02 (=CH), 121.42 (=CH), 128.10 (=CH), 128.80 (=CH), 129.04 (=CH), 130.28 (=CH), 130.82 (=CH), 131.08 (=CH), 131.54 (C-Cl), 133.60 (>C=), 135.24 (=CH), 141.68 (>C=), 144.90 (>C=), 147.40 (>C=).

3-(3-Chloro-phenyl)-8-methoxy-9-methyl-[1,2,4]triazolo[4,3-c]quinazoline (4b)

IR(KBr)ν_{max}: 1203.53(N-N), 1638.98 (C=N), 1585.25 (>C=C<), 3020.08(Ar-CH), 1014.44 (-OCH_3), 698.96 (C-Cl).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 2.35 (s, 3H, -CH_3), 4.12 (s, 3H, -OCH_3), 6.94 (s,1H, =CH), 7.60 (s,1H, =CH), 7.64 (s,1H, =CH), 9.01 (s,1H, =CH).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 16.84 (-CH_3), 92.62 (=CH), 116.98 (>C=),127.60 (>C=),124.72 (=CH), 128.10 (=CH), 128.22 (=CH), 130.44 (=CH), 130.06 (=CH), 130.90 (>C=), 134.60 (C-Cl), 136.02 (=CH), 145.06 (>C=), 147.24 (>C=), 147.40 (>C=), 148.70 (>C=), 156.10 (>C=).

3-(4-Chloro-phenyl)-8,9-dimethoxy-[1,2,4]triazolo[4,3-c]quinazoline (4c)

IR(KBr)ν_{max}: 1216.48(N-N), 1635.10 (C=N), 1514.20 (>C=C<), 3032.92(Ar-CH), 1058.16 (-OCH_3), 698.82 (C-Cl).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 3.92 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.92 (s,1H, =CH), 7.44 (s,1H, =CH), 9.22 (s,1H, =CH), 7.64-7.68 (d,2H, 2 × =CH), 7.64-7.68 (d,2H, 2 × =CH).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 55.82 (-OCH_3), 56.46 (-OCH_3), 94.82 (=CH), 101.68 (=CH), 118.10 (>C=), 122.98 (>C=), 128.48 (2 × =CH), 128.72 (2 × =CH), 134.22 (C-Cl), 135.92 (=CH), 144.21 (>C=), 148.12 (>C=), 148.28 (>C=), 154.22 (>C=), 155.20 (>C=).

3-(4-Hydroxy-phenyl)-8-methoxy-[1,2,4]triazolo[4,3-c]quinazolin-9-ol (4d)

IR(KBr)ν_{max}: 3315.92(C-OH), 1219.44(N-N), 1625.84 (C=N), 1523.98 (>C=C<), 3036.78 (Ar-CH), 1048.84 (-OCH_3).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 3.84 (s, 3H, -OCH_3), 8.82 (s,1H, -OH), 6.84 (s,1H, =CH), 7.48 (s,1H, =CH), 9.22 (s, 1H, =CH), 6.92-7.91 (d,2H, 2 × =CH), 6.92-7.91 (d,2H, 2 × =CH).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 56.10 (-OCH_3), 95.28 (=CH), 102.04 (>C=), 116.10 (2 × =CH), 116.92 (=CH), 130.16 (2 × =CH), 123.02 (>C=), 136.11 (=CH), 144.22 (>C=), 147.62 (>C=), 148.24 (>C=), 148.50 (>C=),149.16(>C=), 157.93 (>C=).

3-(2,4-Dichloro-phenyl)-8-methoxy-9-nitro-[1,2,4]triazolo[4,3-c]quinazoline (4e)

IR(KBr)ν_{max}: 692.48(C-Cl), 1238.65.(N-N), 1632.41 (C=N), 1517.91 (>C=C<), 3048.21(Ar-CH), 1532.66(-NO_2), 1065.34 (-OCH_3).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 4.12 (s, 3H, -OCH_3), 7.50 (s,1H, =CH), 8.90 (s,1H, =CH), 9.12 (s,1H, =CH), 7.80 (s, 1H, =CH), 7.60-7.82 (d,2H, 2 × =CH).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 56.90 (-OCH_3), 95.10 (=CH), 118.92 (=CH), 116.98 ((>C=), 128.48 (=CH), 128.95 (=CH), 129.02 (=CH), 133.32 (C-Cl), 133.51 (>C=), 133.80 (C-Cl), 135.91 (=CH), 136.74(C-NO_2), 148.88 (>C=), 147.78 (>C=), 148.50 (>C=), 152.64 (>C=).

4-(9-Bromo-8-methoxy-[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-benzene-1,2-diol (4f)

IR(KBr)ν_{max}: 653.56(C-Br), 3380.12 (C-OH), 1078.36 (-OCH_3), 1221.86.(N-N), 1632.41 (C=N), 1519.28 (>C=C<), 3082.34(Ar-CH).

H^1 NMR ($CDCl_3$, 200.13MHz): δ 3.98 (s, 3H, -OCH_3), 6.92 (s,1H, =CH), 8.04 (s,1H, =CH), 9.12 (s,1H, =CH), 7.22 (s, 1H, =CH), 8.89 (s, 1H, -OH), 8.89 (s, 1H, -OH).

^{13}C NMR($CDCl_3$, 50.32 MHz): δ 56.64 (-OCH_3), 95.20 (=CH), 113.22 (=CH), 113.42 ((>C=), 116.05 (=CH), 117.21 (>C=), 129.14 (=CH), 129.32 (=CH), 131.32 (>C=), 136.45 (=CH), 144.87 ((>C=), 145.11(C-OH), 147.19 (>C=), 148.91(C-OH), 149.08(>C=), 154.85 (>C=).

RESULT AND DISCUSSION

The present work deals with the preparation of substituted triazolo quinazoline derivatives by three component reaction using microwave irradiation method where, the substituted triazolo quinazolines were prepared by irradiating the 2-amino benzoic acid, amides and hydrazine hydrate for 3.0 to 7.5min.

1) Our experimental protocols have developed an easy, faster and most convenient optimized conditions for preparing new substituted triazolo quinazolines.

2) It has been found that substituted triazolo pyrimidinederivatives were synthesized was obtained with 86 to 92% yield.
3) The structures of [4(a-f)] were established on the basis of their elemental analysis and spectral data (IR, $H^{113}C$ NMR).

CONCLUSION

In conclusion, we have described the synthesis substituted triazoloquinazoline derivatives in excellent yields. The reaction of various 2-aminobenzoic acid with different amide afforded the 7-(substituted phenyl)-6-(substituted phenyl)-3H-quinazolin-4-one derivatives with good yields by microwave irradiation at about 200 power for 2.0 to 7.5 min. which were further reacted with hydrazine hydrate and aromatic aldehyde to furnished 3-(substituted phenyl)-8-(substituted phenyl)-9-(substituted phenyl)-[1,2,4]triazolo[4,3-c]quinazoline in excellent yields with short reaction time. This procedure offers a good scope for the synthesis of a wide variety of substituted triazolopyrimidine derivatives in two steps.

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