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"SYNTHESIS AND ANTIOXIDANT, ANTIMICROBIAL ACTIVITY OF 9-SUBSTITUTED DERIVATIVES OF 6,7-DIHYDRO-6,6-DIMETHYL-9-(4'-PHENYL) TETRAZOLO[5,1-*b*]QUINAZOLIN-8(3*H*,5*H*,9*H*)-ONE."

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ABSTRACT

A green, simple and efficient procedure has been developed for the synthesis of 9-substituted derivatives of 6,7-dihydro-6,6-dimethyl-9-(4'-phenyl) tetrazolo [5,1-*b*] quinazolin-8(3*H*,5*H*,9*H*)-one via a multicomponent one pot three molecule condensation of 1*H*-tetrazol-5-amine, dimedone in acetonitrile and iodine with different substituted aromatic aldehyde . Newly synthesized tetrazolo[5,1-*b*] quinazolin-8(3*H*,5*H*,9*H*)-one derivatives were screened for their antioxidant and antimicrobial activity.

KEYWORDS: 1*H*-tetrazol-5-amine, Dimedone, Aromatic Aldehyde , Molecular iodine, MCR's.

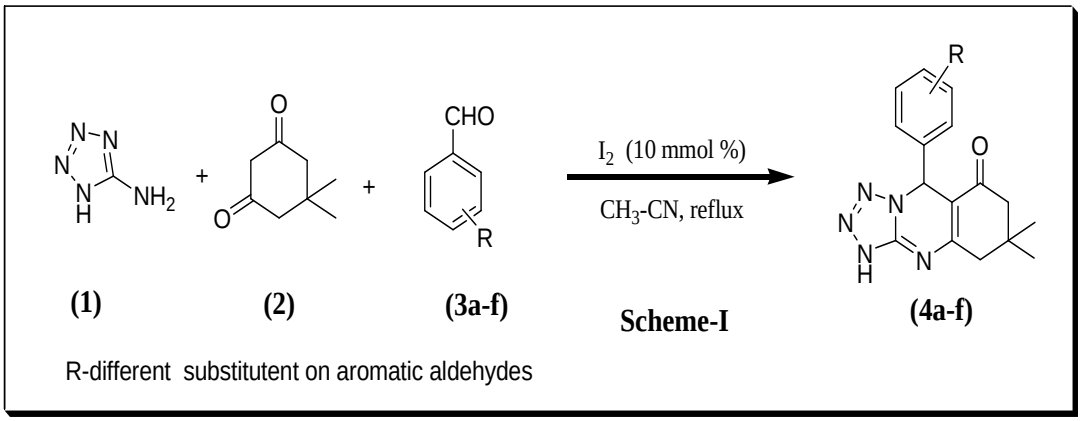
INTRODUCTION

Tetrazolo derivatives have greatly increasing important in nitrogen fused heterocyclic field. The literature survey revealed that tetrazolo [5,1-*b*] quinazolinone derivatives shows potent biological activities and pharmacological activities like antimicrobial[1], antibacterial[2], antifungal[3], anti-inflammatory[4], analgesic[5], anticonvulsant[6], anticancer[7], anti-diabetic[8], antihypertensive[9], hypoglycemic[10], antituberculosis.[11] In addition to these derivatives show diverse application in pharmaceutical industry, agrochemical industry and effectively used as building blocks in several alkaloid compounds.

Now a day, the use of iodine in fused heterocyclic organic compounds has considerable interest as a non-toxic, inexpensive and easily available agent with high selectivity in excellent yield. Owing to advantages associated with eco-friendly iodine and all these wide range of biological activities of different tetrazolo [5,1-*b*]quinazolinone encourage us to synthesis some new derivatives of tetrazolo [5,1-*b*]quinazolinone. So, in this present investigation we report the synthesis of 9-substituted derivatives of 6,7-dihydro-6,6-dimethyl-9-(4'-phenyl)tetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one having potent antioxidant activity.

RESULT AND DISCUSSION

Initially, the reaction mixture of 1*H*-tetrazol-5-amine, (10 mmol) **(1)** and dimedone (10 mmol) **(2)** was refluxed independently in acetonitrile and iodine with different substituted benzaldehydes (10 mmol) **(3a-f)** to isolate the respective 9-substituted derivatives of 6,7-dihydro-6,6-dimethyl-9-(4'-methylphenyl)tetrazolo[5,1-*b*] quinazolin-8 (3*H*,5*H*,9*H*)-one**(4a-f)(Scheme-I).** The progress of the reactions is monitored by TLC. After the completion of the reaction mixture was cooled the precipitate formed was filtered, washed, dried and recrystallized by ethanol.The isolated products **(4a-f)** were completely characterized from IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.



Scheme-I

The formation of compounds **(4a)** was evident & shows IR spectrum in KBr exhibited stretching band at 3170 cm^{-I}, 1465 cm^{-I} for the –NH, medium intensity band at 1654 cm^{-I} for C=O stretching. The ^{1}H-NMR (400 MH$_{Z}$,) was recorded in DMSO, it showed characteristic singlet peak at δ 6.56 ppm and mass spectra(ESI) shows peak at 310 ($M^{+\cdot}$ +1, 100%) and ^{13}C-NMR (400 MH$_{Z}$) in DMSO.

The molecular iodine has acting remarkable reagent properties like hard-soft reagent that's why reaction mechanism was accelerated.[12] On the basis of all our experimental analysis result. We proposed tentative plausible mechanism for the formation of tetrazolo [5, 1-*b*]quinazolinone derivatives **(4a-e)** in the presence of molecular iodine. The hypothesis supported the fact that reaction initiated from iodine. The overall, mechanism takes place according to Knoevenagels-Micheal reaction.**(Scheme-II)**

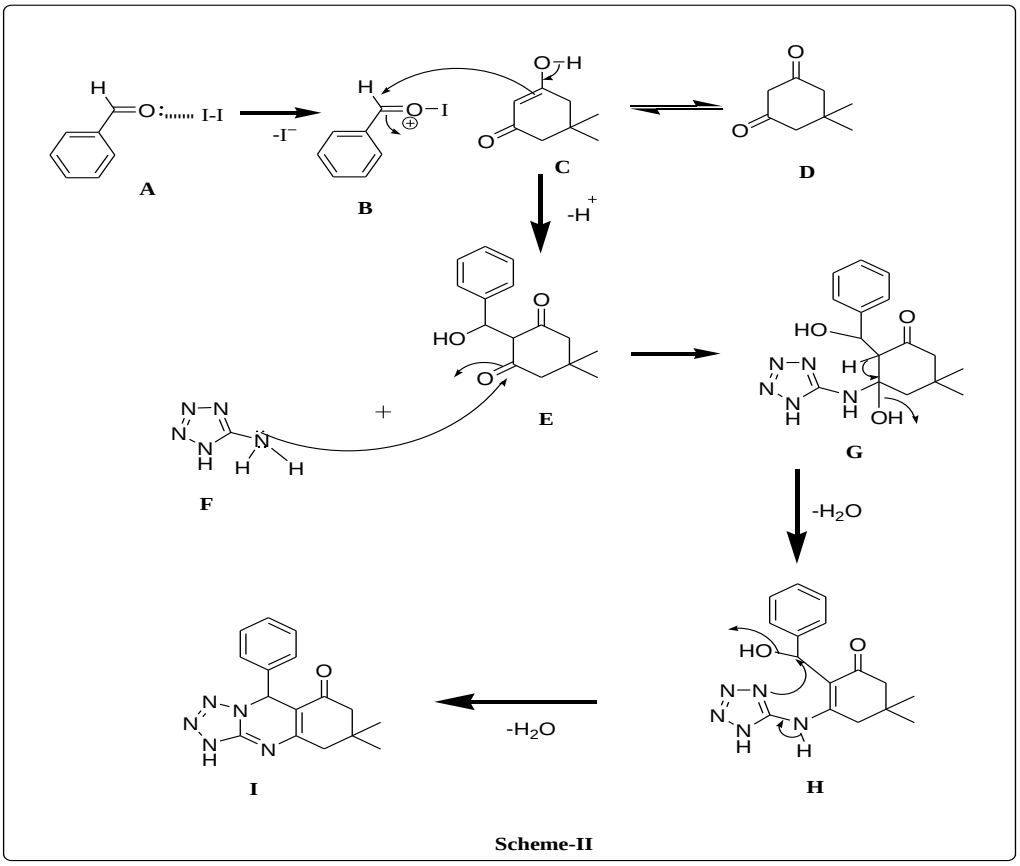


Table 1: Multicomponent reaction of 1*H*-tetrazol-5-amine (1), dimedone (2), and aromatic aldehyde (3a-e), for the synthesis of 4a-4f.

Entry	Subst. Aldehyde (Ar)	Products	Time (Hrs)	Yield%	M.P.^{0}C
1	4-CH_3 -C_6H_4	**4a**	3.0	73	230-232
2	4-OCH_3 -C_6H_4	**4b**	3.0	65	210-212
2	4-OH- C_6H_4	**4c**	3.5	67	217-219
3	3,4-diOCH_3-C_6H_3	**4d**	3.5	70	244-247
4	2,4-diCl -C_6H_3	**4e**	4.0	68	250-252
5	4- OH,3-OCH_3 -C_6H_3	**4f**	2.5	69	209-211

EXPERIMENTAL

Open capillary tubes were used for melting points of isolated synthesized compounds and are uncorrected. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of

compounds. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on various spectrometers at 400MHz using TMS as an internal standard.

General procedure for the synthesis of 9-substituted derivatives of 6,7-dihydro-6,6-dimethyl-9-(4'-phenyl)tetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one(4a-e).

An equimolar mixture of 1*H*-tetrazol-5-amine, dimedone and different substituted benzaaldehydes **(3a-f)** was refluxed independently in the presence of molecular iodine (10 mol %) in acetonitrile (10 ml) for 2-4 hours. The reaction mass was cooled at room temperature and poured into ice cold water .The solid obtained was filtered, washed and recrystallized by ethanol to give the**(4a-f)** compounds. The reaction was monitored by TLC.

Spectral Analysis

6,7-dihydro-6,6-dimethyl-9-p-tolyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one (4a)

M.P. 230-232 ^{0}C, Yield 73% .IR (KBr / cm^{-1}) 3170 (=NH),1650 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 1.07 -1.96 (2s, 6H, -2CH_3), δ 2.12-2.16 (dd, 2H, -CH_2) , δ 2.25 (s, 2H, -CH_2), δ 2.61(s, 3H, Ar-CH_3), δ 6.56 (s, 1H, -CH), δ 7.09-7.19 (m, 4H, Ar-H), δ 11.75 (s, 1H, -NH) ; EI-MS (m/z: RA %): 310 (M^+ + 1, 100%). ^{13}C NMR (400 MHz, DMSO–d_6/ppm) δ 26.9, 28.3, 57.1, 126.9, 128.9, 137.4,148.4, 150.1, 192.7. Elemental analysis calculated data for $C_{17}H_{19}N_5O$; C, 66.00; N, 22.64. Found: C, 65.98; N, 22.62.

6,7-dihydro-9-(4'-methoxyphenyl)-6,6-dimethyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one (4b)

M.P. 210-212^{0}C, Yield 65%. IR (KBr/ cm^{-1}) 3388 (=NH),1631 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 1.03 -1.10 (2s, 6H, -2CH_3), δ 2.04-2.26 (dd, 2H, -CH_2) , δ 2.45 (s, 2H, -CH_2), δ 3.44(s, 1H, -OCH_3), δ 6.58 (s, 1H, -CH), δ 7.15-7.33(m, 4H, Ar-H), δ 11.75 (s, 1-NH); EI-MS (m/z: RA %): 326 (M^+ + 1,100%). Elemental analysis calculated data for $C_{17}H_{19}N_5O_2$; C, 62.75; N, 21.52. Found: C, 62.73; N, 21.50.

6,7-dihydro-9-(4'-hydroxyphenyl)-6,6-dimethyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one (4c)

M.P. 217-219^{0}C, Yield 67% .IR (KBr/ cm^{-1}) 3390 (-OH); 3224 (=NH),1647 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 0.64 -0.79 (2s, 6H, -2CH_3), δ 2.21-2.27 (dd, 2H, -CH_2) , δ 2.30 (s, 2H, -CH_2), δ 2.34 (s, 1H, -OH), δ 6.25 (s, 1H, -CH), δ 6.47-6.86 (m,4H,Ar-H), δ

11.27 (s, 1-HN); EI-MS (m/z: RA %): 311 (M^+ + 1,100%). Elemental analysis calculated data for $C_{16}H_{17}N_5O_2$; C, 61.72; N, 22.49. Found: C, 61.70; N, 22.47.

6,7-dihydro-9-(3',4'-dimethoxyphenyl)-6,6-dimethyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)–one (4d)

M.P. 244-247^{0}C, Yield 70%. IR (KBr/ cm^{-1}) 3166 (=NH),1654 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 1.07 -1.11 (2s, 6H, -2CH_3), δ 2.13-2.19(dd, 2H, -CH_2) , δ 2.46 (s, 2H, -CH_2), δ 3.57 -3.77(2s, 6H, -2OCH_3), δ 6.54 (s, 1H, -CH), δ 6.77-6.82 (m, 2H, Ar-H), δ 6.89 (d, 1H, Ar-H), δ 11.50 (s, 1-HN); EI-MS (m/z: RA %): 355 (M^{+1} 100%). ^{13}C NMR (400 MHz, DMSO–d_6/ppm) δ: 26.8, 28.5, 32.2,49.9,57.3, 105.6, 110.7,119.2, 132.6, 148.2, 128.9, 148.4,150.1, 192.8. Elemental analysis calculated data for $C_{18}H_{21}N_5O_3$; C, 60.83; N, 19.71. Found: C, 60.81; N, 19.69.

9-(2',4'-dichlorophenyl)-6,7-dihydro-6,6-dimethyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)-one(4e)

M.P. 250-252^{0}C, Yield 68% . IR (KBr/ cm^{-1}) 3170 (=NH),1650 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 1.04-1.09(2s, 6H, -2CH_3), δ 2.05-2.25 (dd, 2H, -CH_2) , δ 2.54 (s, 2H, -CH_2), δ 6.90 (s, 1H, -CH), δ 7.33-7.56 (2d, 2H,Ar-H), δ 7.68 (s, 1H,Ar-H), δ 11.75 (s, 1-HN); EI-MS (m/z: RA %): 364 (M^{+1} 100%),366(M^+ +2,33%). ^{13}C NMR (400 MHz, DMSO–d_6/ppm) δ: 27.0, 55.3, 78.8,79.0, 104.1, 127.4, 130.7, 148.2, 151.2, 192.8. Elemental analysis calculated data for $C_{16}H_{15}Cl_2N_5O$; C, 52.76; N, 19.23. Found: C, 52.74; N, 19.21.

6,7-dihydro-9-(4'-hydroxy-3'-methoxyphenyl)-6,6-dimethyltetrazolo[5,1-*b*]quinazolin-8(3*H*,5*H*,9*H*)–one (4f)

M.P. 209-211^{0}C, Yield 69%.IR (KBr/cm^{-1}) 3382 (-OH); 3266 (=NH),1684 (C=O); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 1.01-1.09 (2s, 6H, -2CH_3), δ 2.05-2.25 (dd, 2H, CH_2) , δ 2.54 (s, 2H, CH_2), δ 2.46(s, 1H, -OH), δ 3.40(s, 3H, -OCH_3), δ 6.63 (s, 1H, -CH), δ 7.12-7.37 (m, 3H,Ar-H), δ 11.63 (s, 1-NH); EI-MS (m/z: RA %): 342 (M^{+1} 100%). Elemental analysis calculated data for $C_{17}H_{19}N_5O_3$; C, 59.81; N, 20.52. Found: C, 59.79; N, 20.50.

BIOLOGICAL ACTIVITY

Antioxidant Activity

DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging assay

DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging assay was proceed by reported method.[13] Take 1 ml (1 mM) of the test sample is added to equimolar quantity of 0.1 mM

solution of DPPH in ethanol. After incubation at room temperature for 25 min, then the DPPH reduction was takes places and measured by Reading the absorbance at 517 nm. Ascorbic acid (1mM) used as reference compound.

The compound **(4e, 4d)** showed remarkable antioxidant activity against DDPH radical scavenging activity with reference of ascorbic acid.

Table 2: Antioxidant activity of tested compounds (4a-4f.)

Entry	Compounds	Antioxidant Activity
		DPPH radical scavenging activity (%)
1	4a	59 ± 0.40
2	4b	61 ± 0.58
3	4c	68 ± 0.38
4	4d	71 ± 0.59
5	4e	79 ± 0.68
6	4f	66 ± 0.61
7	**Ascorbic acid (Vit. C)**	**80 ± 0.86**

Antimicrobial activity

The synthesized compounds were evaluated for their antibacterial activity against gram positive species *S. aureus* and *B.subtilis* and gram negative species *E.coli* and *S.typhi* by paper diffusion method. All the synthesized compounds were dissolved in dimethyl sulphoxide (DMSO). The synthesized compounds exhibited zone of inhibition at 07-14mm in diameter where as standard Norfloxacin exhibited zone of inhibition at 14 and 24 in diameter against *S. aureus* and *B.subtilis* and 20 and 16mm in diameter against *E.coli* and *B.subtilis* and 20 and 18mm in diameter against *S. aureus* and *B.subtilis* respectively. Amongst the synthesized compounds **(4e)** shows higher zone of inhibition against *S. aureus*. Compounds **(4b, 4d, 4e)** shows higher zone of inhibition against *E.coli*, compounds **(4d, 4e)** shows higher zone of inhibition against *B.subtilis* and *S. aureus* shows higher zone of inhibition against *S.typhi* as compaired to other compounds.

Table 3: Antimicrobial activity of compound (4a-4f).

Entry	Compounds	Zone of Inhibition in mm			
		S.aureus	***B.subtilis***	***E.coli***	***S.typhi***
1	4a	08	14	12	10
2	4b	10	**18**	14	08
3	4c	08	12	10	12
4	4d	12	10	**15**	13
5	4e	**13**	**20**	**18**	**16**

6	4f	09	10	12	08
7	**Norfloxacin**	**14**	**24**	**20**	**16**
8	**Streptomycin**	**16**	**18**	**20**	**18**

CONCLUSION

In conclusion, we have synthesized an efficient and facile method of 9-substituted derivatives of 6,7-dihydro-6, 6-dimethyl -9-(4'-methylphenyl) tetrazolo [5,1-*b*] quinazolin-8(3*H*,5*H*,9*H*)–one by reaction of corresponding aldehyde, 1*H*-tetrazol-5-amine and dimedone in presence of molecular iodine in acetonitrile. The product can be easily isolated by simple workup technique, requires ambient reaction condition, less expensive, short time and give excellent yield. Among these synthesized compounds few compounds shows potent antioxidant as well as antimicrobial activity.

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