Synthesis, Characterization, and *in Vitro* Antimicrobial Screening of Some Novel Heterocycles Linked to Tetrazolo [5,1-*f*]-1,2,4-Triazine Moiety

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ABSTRACT:
8-Hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine **(1)** reacted with one or two carbon cyclizing reagents to yield various heterocyclic systems. Some of the representative members of the prepared compounds were screened for antimicrobial assessment.

Keywords: 8- Hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine, heterocycles, *in Vitro* antimicrobial activity

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INTRODUCTION

The tetrazole nucleus of several compounds has been received[1-11] much great attention because of their wide range of therapeutic and biological activities.[12.13] Compounds containing tetrazole core have diverse biological activities as antibacterial,[1,3-9,14] antiproliferation,[15] anticancer,[15] and anticonvulsant[16] agents. In view of the aforementioned facts, it seemed most interesting to synthesize some condensed or uncondensed 8-hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine with the aim to evaluate their antimicrobial activities.

RESULTS AND DISCUSSION

Condensation of 8-hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine **(1)** with equimolar amount of the appropriate aromatic namely : benzaldehyde, *p*-tolylbenzaldehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde in boiling methanol afforded the corresponding 8-arylidenehydrazinotetrazolo[5,1-*f*]-1,2,4-triazines **2a-d** (Scheme 1), showing the expected NH in **IR** absorption as well as **^{1}H NMR** signals characteristic of NH (D_2O-exchangeable), methylenic (-CH=N-), and aromatic protons. Their **MS** revealed the correct molecular ion peaks which were supported by elemental analyses. Subjecting these hydrazone derivatives **2a-d** to dehydrogenative cyclization with bromine in glacial acetic acid in the presence of anhydrous sodium acetate yielded the corresponding 8-aryl-1,2,4-triazolo[4,3-*d*]tetrazolo[5,1-*f*]-1,2,4-triazines **3a-d**. These structures lacked the NH absorption in **IR** and methylenic proton signal in **^{1}H NMR**. In addition, the chemical proof for the assigned compounds **3a-d** were also prepared of hydrazine **1** with the equimolar amount of the corresponding aromatic acid chloride using phosphorus oxychloride through the un-isolable aroylhydrazino – intermediates **[A]** which were formed and concomitantly dehydratively cyclized. The aforementioned products **3a-d** were proved to be identical in all respects (mp; mixed mp; TLC; and **IR**) with methods of cyclization mentioned above this article. Recently[1], the products **3a-d** gave directly by the reaction of 8-chloro tetrazolo[5,1-*f*]-1,2,4-triazine with corresponding of aromatic acid hydrazides. Elemental and spectra data of these products are consistent with the structure asigned above two cyclization reactions.

Refluxing of hydrazine **1** with excess of ethyl chloroformate in pyridine afforded a product, which showed neither ester-carbonyl absorption in **IR** nor ethyl group signal in **^{1}H NMR**. None of the possible intermediate **[B]** (Scheme 1) was isolated but showed NH and CON absorptions in **IR** and was consequently, assigned the structure 1,2,4-triazolo [4,3-*d*]tetrazolo[5,1-*f*]-1,2,4-triazin-8-(9H)-one **(4)**

Condensation of cyclic amidrazone **1** with pyruvic acid at ambient temperature or heating at 100^{o}C resulted in the corresponding hydrazone **5a**, which possessed **IR** characteristic of OH, NH, and CO absorptions. Similarly, ethyl pyruvate reacted with the hydrazine **1** to furnish the corresponding hydrazone **5b**, **^{1}H NMR** spectrum of the latter contained the quartet and triplet pattern signals characteristic of ethyl group (*cf.* Experimental). Acid-induced heterocyclization of **5a** or **5b** (Scheme 1) by heating under reflux in acetic acid provided one and the same product, which displayed the disappearance of OH and NH absorptions but showed a CON absorption in **IR** region. The **^{1}H NMR** spectrum of this cyclization product revealed no ethyl pattern. These data together with correct elemental analysis are compatible the structure 9-methyltetrazolo [5,1-*f*]-1,2,4-triazino[4,3-*d*]-1,2,4-triazin-8-one **(6)**. The mass spectrum of **6** showed a peak corresponding to its

molecular ion at *m/z* =204 ($C_6H_4N_8O$).

Condensative cyclization of **1** with equimolar amount of diethyl oxalate (Scheme 2) furnished the corresponding tetrazolo[5,1-*f*]-1,2,4-triazino[4,3-*d*]-1,2,4-triazine-8,9-(10H)-dione (**7**). Assignment of the latter structure and exclusion the possible non-isolable intermediate **[C]** was established by correct elemental analysis as well as the absence of quartet-triplet pattern of **^{1}H NMR** signals characteristic an ethyl group. Also, the mass spectrum of compound **7** caused molecular ion peak (*m/*z = 206) in agreement with its molecular formula ($C_5H_2N_8O_2$).

Furthermore, Condensation of the hydrazine **1** with acetylacetone (Scheme 2) was heated under reflux yielded the corresponding hydrazone derivative **8a** which showed **IR** absorptions characteristic of NH and CO, and **^{1}H NMR** spectrum of the latter product revealed the presence of NH (D_2O-exchangeable), methylene and two methyl group signals. Heating of **8a** with glacial acetic acid resulted in the cyclization to the 8-(3,5-dimethylpyrazol-1-yl) tetrazolo[5,1-*f*]-1,2,4-triazine system **(9a)** which revealed only C=N absorption and lacked NH and CO absorptions characteristic of the parent hydrazone **8a**, and appeared pyrazolyl CH proton signal in the **^{1}H NMR** spectrum.

Likewise, condensation of ethyl acetoacetate with cyclic amidrazone **1** (Scheme 2) provided formation the isoable hydrazone intermediate **8b**, which underwent base catalyzed cyclization upon refluxing with 0.1M sodium ethoxide to build either the pyrazolyl derivative **9b** or 8-methyl -1,2,4-triazolo[4,3-*d*]tetrazolo[5,1-*f*]-1,2,4-triazine structure (**10**, Scheme 2) according to a reported[5] result which synthesized *via* the reaction of **1** with acetic acid. Structures elucidation of **9b** or **10** were based through the elimination an ethyl alcohol or an ethyl acetate molecule, respectively, from **8b** compound. Thus, the evidences of the cyclization of the hydrazone **8b** are: (a) the melting point and thin layer chromatography of the performed cyclization product are not similar to the structure **10**[5] (mp 219-221^{o}C); **9b** (mp 235-237^{o}C) and (b) spectroscopic data of the product **9b** showed OH and lacked any amide absorption bands in the **IR** region; **^{1}H NMR** exhibited OH (D_2O-exchangeable) and pyrazolyl CH proton signals. Accordingly, the product was decisively assigned as the 8-(5-hydroxy-3-methylpyrazol-1-yl)tetrazolo[5,1-*f*]-1,2,4-triazine **(9b)** and formation the structure **10** could be excluded thereby. This is in accordance with the previous reports,[17,18] but contradict another[19] one on the reaction of ethyl acetoacetate with different cyclic amidrazones.

EXPERIMENTAL

General

Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions were followed up and the purification of products was carried out on pre-(layer thicickness 0.25mm; coated TLC plates Silica Gel-Merck), visualizin the spots in Iodine. **IR** spectra were recorded (KBr) on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The **^{1}H NMR** spectra were determined in *DMSO*(d_6) at 300 MHz on a Varian Mercury VX 300 NMR spectrometer and their chemical shifts (δ/ppm) are reported using *TMS* as internal standard. Mass spectra were recorded on a HP model **MS** 5988 spectrometer at electron ionizing energy of 70 ev. Microanalyses were performed by the Microanalytical Unit, Cairo University, Egypt; the obtained results agreed satisfactorily with the calculated values.

*Synthesis of 8-arylidenehydrazinotetrazolo[5,1-f]-1,2,4-triazines **2a-d** (General Procedure)*

A solution of 6 mmol of **1** in 15 cm^3 methanol was added to 6 mmol appropriate aromatic aldehyde and the mixture was heated at 100°C for 10 min. The reaction mixture was kept at ambient temperature for overnight and the product which separated was filtered off, washed with ether, dried, and crystallized from methanol. The physico-chemical and spectra data of **2a-d** the following:

8-Benzylidenehydrazinotetrazolo[5,1-f]-1,2,4-triazine **(2a,** $C_{10}H_8N_8$)

Yield: 1.32g (83.54%); pale yellow; mp 158-160°C; **IR**: γ=3325 (NH), 1625 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=11.60 (s, 1H, D_2O-exchangeable NH), 8.20-7.90 (m, 5H, *Ar* H), 7.61 (s, 1H, methylenic H) 5.90 (s, 1H, CH) ppm; **MS**: *m/z* (%) = 240 (M^+, 15), 241 (M^++1, 18).

8-p-Tolylmethylidenehydrazinotetrazolo[5,1-f]-1,2,4-triazine **(2b,** $C_{11}H_{10}N_8$)

Yield: 1.42g (83.03%); yellow; mp 160-162°C; **IR**: γ=3340 (NH), 1610 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=10.87 (s, 1H, D_2O-exchangeable NH), 8.17-7.82 (m, 4H, *Ar* H), 7.71 (s, 1H, methylenic H), 5.89 (2, 1H, CH), 2.30 (s, 3H, CH_3) ppm; **MS**: *m/z* (%) = 254 (M^+, 30).

8-p-Chlorobenzylidenehydrazinotetrazolo[5,1-f]-1,2,4-triazine **(2c,** $C_{10}H_7ClN_8$)

Yield: 1.42g (78.45%); yellow; mp 1701-172°C; **IR**: γ=3350 (NH), 1610 (C=N) cm^{-1} **MS**: *m/z* (%) = 275 (M^+, 16).

8-p-Nitrobenzylidenehydrazinotetrazolo[5,1-f]-1,2,4-triazine **(2d,** $C_{10}H_7N_9O_2$)

Yield: 1.52g (81.07%); orange; mp 190-192°C; **IR**: γ=3340 (NH), 1630 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=10.68 (s, 1H, D_2O-exchangeable NH), 8.31-7.74 (m, 4H, *Ar* H), 7.22 (s, 1H, methylenic H), 5.75 (s, 1H, CH) ppm; **MS**: *m/z* (%) = 285 (M^+, 20).

*Synthesis of 8-aryl-1,2,4-triazolo[4,3-d]tetrazolo[5,1-f]-1,2,4-triazine **3a-d** (General Procedure)*

Method A. To a solution of 4 mmol of the respective hydrazone **2a-d** in 15 cm^3 glacial acetic acid containing 4 mmol bromine in 10 cm^3 glacial acetic acid were added gradually with stirring. The reaction mixture was then warmed on a boiling water-bath for 5 min, left to cool and then poured onto water. The precipitated solid was filtered off, washed thoroughly with water, and crystallized from methanol.

Method B. A mixture of hydrazine **1** (6 mmol), particular aromatic acid chloride (6 mmol), and 10 cm^3 phosphorus oxychloride was refluxed for 1h, then cooled and poured onto of 30 cm^3 cold saturated solution of sodium bicarbonate. The crude solid that precipitated was filtered off, washed with water, dried, and finally crystallized from methanol.

Method C[1]. A mixture of **1** (6 mmol) and appropriate aromatic acid hydrazide in ethanol (30 cm^3) was refluxed for 3h, after cooling the mass product was filtered off and recrystallized from abs. ethanol.

The aforementioned methods **A**, **B**, and **C** are compatible with the assigned products **3a-d**.

1,2,4-Triazolo[4,3-d]tetrazolo[5,1-f]-1,2,4-triazin- 8-(9H)-one **(4,** $C_4H_2N_8O$)

A suspension of **1** (6 mmol) in 2 cm^3 pyridine was treated with excess of ethyl chloroformate and the mixture was treated under reflux for 3h. The reaction mixture was poured onto ice-water and the product which separated was filtered off, washed with water, and crystallized from methanol. Yield: 0.85g (72.65%); mp 210°C; **IR**: γ=3300 (NH), 1690 (CON), 1625 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): δ=11.85 (s, 1H, D_2O-exchangeable), 5.75 (s, 1H, CH) ppm; **MS**: *m/z* (%) = 178 (M^+, 26).

*Synthesis of **5a** and **5b** (General Procedure)*

To a solution of **1** (6 mmol) in 10 cm^3 methanol, 6 mmol pyruvic acid or ethyl pyruvate were added and the mixture was kept at ambient temperature for 24h or heated at reflux for 1h. The product which separated was filtered off, washed with ether, and crystallized from methanol to provide **5a** and **5b**.

Pyruvic acid {tetrazolo[5,1-f]-1,2,4-triazin-8-yl} hydrazone (**5a**, $C_6H_6N_8O_2$)

Yield: 0.92g (68.49%); mp 175°C; **IR**: γ=3450 (OH), 3225 (NH), 1715 (C=O), 1625 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): δ=12.52 (s, 1H, D_2O-exchangeable OH), 11.84(s, 1H, D_2O-exchangeable NH), 5.90 (s, 1H, CH), 2.50(s, 3H, CH_3) ppm; **MS**: *m/z* (%) = 223 (M^++1, 27).

Ethyl pyruvate {tetrazolo[5,1-f]-1,2,4-triazin-8-yl} hydrazone (**5b**, $C_8H_{10}N_8O_2$)

Yield: 1.31g (79.39%); mp 185°C; **IR**: γ=3210 (NH), 1730 (C=O), 1600 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): δ=11.61 (s, 1H, D_2O-exchangeable NH), 5.85 (s, 1H, CH), 3.85 (q, 2H, CH_2CH_3), 2.55 (s, 3H, CH_3), 1.35 (t, 3H, CH_2CH_3) ppm; **MS**: *m/z* (%) = 250 (M^+, 30).

9-Methyltetrazolo [5,1-f]-1,2,4-triazino [4,3-d]-1,2,4-triazin-8-one (**6**, $C_6H_4N_8O$)

A mixture of **5a** or **6b** (4 mmol) and 10 cm^3 acetic acid was heated under reflux for 2h and then evaporated to dryness. The obtained residue was crystallized from methanol. Yield: 0.61g (66.30%); mp 220°C; **IR**: γ=1690 (CON), 1620 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): δ=5.90 (s, 1H, CH), 2.60 (s, 3H, CH_3) ppm; **MS**: *m/z* (%) = 204 (M^+, 33).

Tetrazolo [5,1-f]-1,2,4-triazino [4,3-d]-1,2,4-triazin-8,9-(10 H)-dione (**7**, $C_5H_2N_8O_2$)

A mixture of 1 (6 mmol) and diethyl oxalate (6 mmol) was heated for 1h 100°C. after attaining room temperature, the mixture was triturated with methanol and the product which separated was filtered off and crystallized from methanol. Yield: 0.93g (68.38%); mp 250°C; **IR**: γ=3325 (NH), 1690, 1660 (CON), 1590 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): δ=12.10 (s, 1H, D_2O-exchangeable NH), 5.75 (s, 1H, CH) ppm ; **MS**: *m/z* (%) = 206 (M^+, 19).

*Synthesis of **8a** and **8b** (General Procedure)*

To a solution of **1** (6 mmol) in 15 cm^3 methanol was added to 6 mmol acetylacetone or ethyl acetoacetate and the mixture was heated under reflux for 2h. The separated product was filtered off, washed with ether and crystallized from methanol to perform **8a** and **8b**.

Acetylacetone {tetrazolo[5,1-f]-1,2,4-triazin-8-yl} hydrazone (**8a**, $C_8H_{10}N_8O$)

Yield: 1.13g (73.38%); mp 175°C; **IR**: γ=3240 (NH), 1700 (C=O), 1625 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=11.85 (s, 1H, D_2O-exchangeable NH), 5.80 (s, 1H, CH), 4.12 (s, 2H, CH_2), 2.35, 2.20 (2s, 3H each, $2CH_3$) ppm; **MS**: *m/z* (%) = 234 (M^+, 18).

8-(3,5-Dimethylpyrazol-1-yl) tetrazolo[5,1-f]-1,2,4-triazine (**9a**, $C_8H_8N_8$)

A solution of **8a** (4 mmol) in 10 cm^3 glacial acetic acid was heated under reflux for 2h and then evaporated dryness under reduced pressure. The obtained residue was crystallized from methanol; Yield: 0.53g (57.61%); mp 195-197°C; **IR**: γ=1625 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=5.75 (s, 1H, CH), 5.25 (2, 1H, pyrazolyl CH), 2.30, 2.25 (2s, 3H each, $2CH_3$) ppm ; **MS**: *m/z* (%) = 216 (M^+, 7).

*Ethyl acetoacetate {tetrazolo[5,1-f]-1,2,4-triazin-8-yl} hydrazone (**8b**, $C_9H_{12}N_8O_2$)*

Yield: 1.22g (70.12%); mp 190-192°C; **IR**: γ=3295(NH), 1735 (C=O), 1615 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=12.15 (s, 1H, D_2O-exchangeable NH), 5.78 (s, 1H, CH), 4.20 (q, 2H, CH_2CH_3) 4.10 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.28 (t, 3H, CH_2CH_3) ppm ; **MS**: *m/z* (%) = 265 (M^++1, 8).

8-(5-Hydroxy-3-methylpyrazol-1-yl) tetrazolo[5,1-f]-1,2,4-triazine (**9b**, $C_7H_6N_8O$)

A solution of **8b** (3 mmol) in 15 cm^3 freshly prepared 0.1M sodium ethoxide was heated under reflux for 2h. The resulting solution was neutralized with acetic acid and product which separated was filtered off and crystallized from methanol; Yield: 0.54g (65.85%); mp 235-237°C; **IR**: γ=3400 (OH), 1615 (C=N) cm^{-1}; **^{1}H NMR** (*DMSO*-d_6): *δ*=12.35 (s, 1H, D_2O-exchangeable OH), 5.80 (s, 1H, CH), 5.30, (s, 1H, pyrazolyl CH), 2.35 (s, 3H, CH_3) ppm ; **MS**: *m/z* (%) = 218 (M^+, 30).

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some the synthesized compounds was determined *in vitro* against a variety of bacteria. The tests were carried out using disc diffusion method[20,21] against *Gram*-positive bacteria and *Gram*-negative bacteria were dissolved in *DMF*, and activity mentioned on 1000 ppm. Agar plates were surface inoculated uniformly from fresh broth culture of the *Gram* bacteria. The discs were incubated at 25°C for 1h to permit good diffusion then incubated at 28°C for 24h, and the zones of inhibition were measured and displayed in **Table** .

Table: Antimicrobial activity of some synthesized compounds

Test compound	Actibacterial activvity			
	Gram +ve bacteria		*Gram-ve* bacteria	
	Baillus subtilis	*Streptococci*	*Klebsiella Pneumoniea*	*Escherechia Coli*
2a	++	++	+	+
2b	+	+	++	++
2d	+++	+++	++	+++
3a	+	+	-	+
3b	++	++	++	++
3d	+++	+++	++	+++
4	+	+	-	-
5a	+	+	+	+
5b	++	++	++	++
6	+	-	-	-
7	-	-	+	+
8a	++	++	+	-
8b	+++	+++	-	-
9a	+++	+++	+++	+++
9b	-	-	+	+
Control DMF	-	-	-	-

The data obtained from above table indicate the compounds **2d**, **3d**, **8b**, and **9a** are higher activity but **5b**, **8a** are moderate activity and some of compound exhibit lower or no activity against *Gram* bacteria.

CONCLUSION

In this article we reported the synthesis of some novel heterocycles starting from 8-hydrazinotetrazolo[5,1-*f*]-1,2,4-triazine **(1)**. Investigation of their antimicrobial activity revealed that **2d**, **3d**, **8b**, and **9a** were the most active compounds although the activity was significantly less than that of the positive control.

REFERENCES

1. Taha, M.A.M. *Int. J. Adv. Res. Chem. Sci.* **2017**, *4*, 43.

2. (a) Gein, V. L.; Zamaraeva, T. M.; Dmitriev, M. V., *Russ. J. Org. Chem.,* **2016**, *52* 558. (b) Golobokova, T. V.; Vereshchagin, L. I., Ratovskii, G. V.; Proidakov, A. G.; Kizhnyaev, V. N. *Ibid.* **2016**, *52*, 1039.

3. El Badry, S. M.; Taha, M. A. M. *J. Korean Chem. Soc.* **2014**, *58*, 381.

4. El-Badry, S.M.; Taha, M.A.M. *J. Korean. Chem. Soc.* 2011, *55*, 974.

5. Taha, M.A.M.; El-Badry, S.M. *J. Korean. Chem. Soc.* **2010** , *54*, 414.

6. Taha, M.A.M.; El-Badry, S.M. *Monatsh. Chem.* **2008**, *139*, 1261.

7. Taha, M.A.M. *Phosphorus, Sulphur, Silicon Relat. Elem.* **2008**, *183*, 2525.

8. Taha, M.A.M. *Monatsh. Chem.* **2007**, *138*, 505.

9. Taha, M.A.M.; El-Badry, S.M. *Phosphorus, Sulfur, Silicon Relat Elem* **2007**, *182*, 1011.

10. Taha, M.A.M.; El-Badry, S.M. *J. Chin. Chem. Soc.* **2006**, *53*, 1181.

11. Taha, M.A.M. *J. Chin. Chem. Soc.* **2005**, *52*, 137.

12. Moderhack, D. *J. Prakt. Chem.***1998**, *340*, 687.

13. Kolodobskii, G. I.; Ostrovskii, V. A.; Popavskii, V. S. *Chem. Heterocycl. Cpds.* **1981**, *17*, 965.

14. Karnik, A.V.; Malviya, N.J.; Kulkarni, A.M.; Jadhav, B.L. *Eur. J. Med. Chem.* **2006**, *41*, 891.

15. Jantova, S.; Ruzekova, I.; Stantovsky, S.; Spirkova, K. *Neoplasma* **1997**, *44*, 240.

16. Rubat, C.; Coudert, P.; Couquelet, J.M.; Tronche, P.; Bastide, J.; Bastide, P. *Formaco* **1990**, *45*, 331.

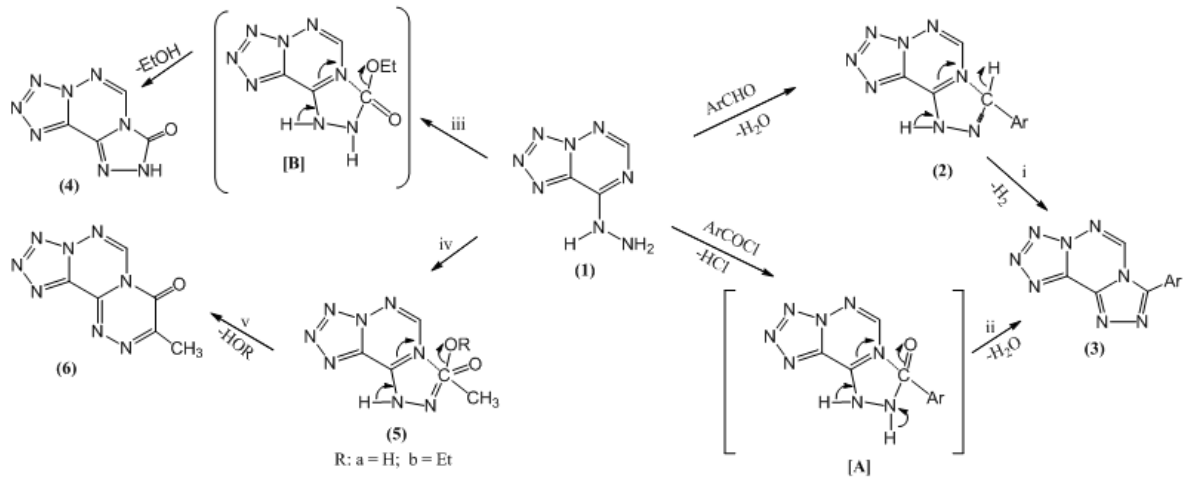
17. Shaban, M.A.E.; Taha, M.A.M; Hamaouda, H.M.A. *Heterocyclic Commun.***1998**, *4*, 351.

18. Shaban, M.A.E.; Taha, M.A.M; Nasr, A.Z.. *Heterocyclic Commun.***1998**, *4*, 473.

19. Shaban, M.A.E., Taha, M.A.M., Nasr, A.Z. *Pharmazine*, **1991**, *46*, 105.

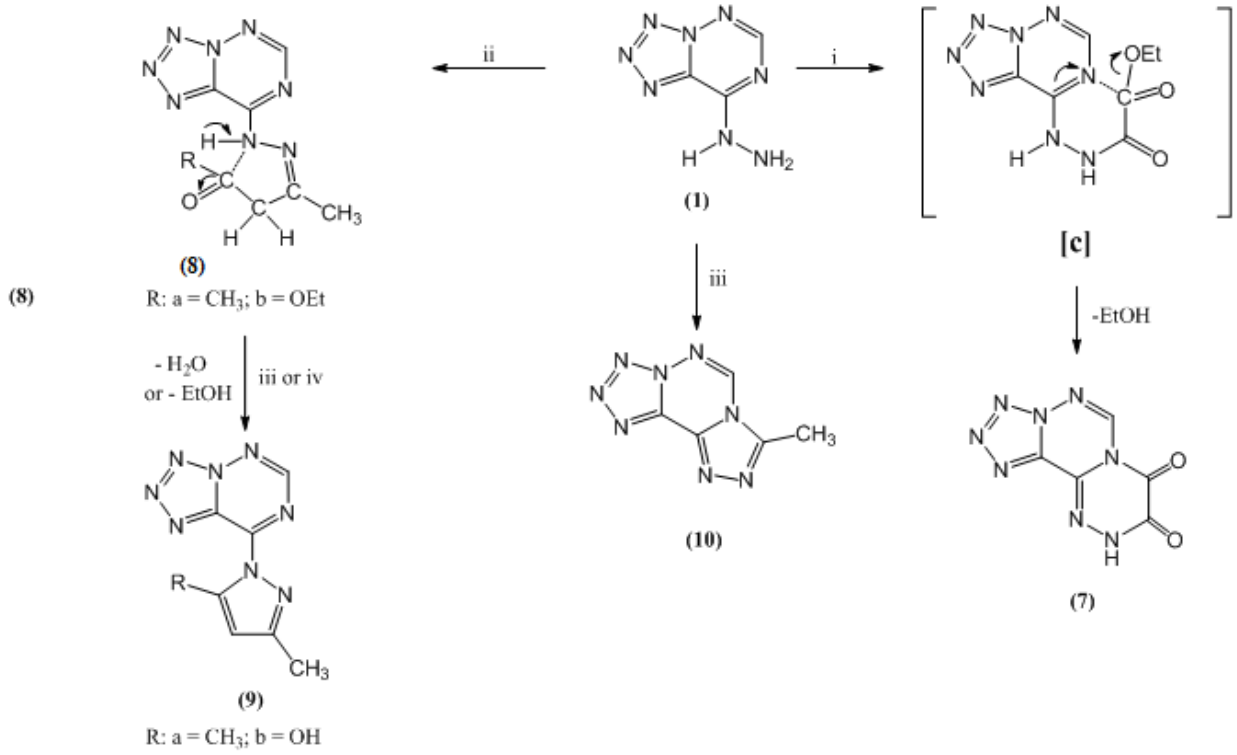
20. Colle, G.J.; Fraser, G.A.; Marmion, P.B.; Simmons, A. *Practical Medical Microbiology,* 14th Edn., Churchill Livingstone: Edinburgh, **1996**, *11*, 163.

21. Arthington, B.A.; Motley, M.; Warmock, D.W., Morrison, C.J. *J. Clin. Microbiology*, **2000**, *38*, 2254.



Reagents: i, Br_2/AcOH; ii, $POCl_3$; iii, ClCOOEt; iv, $CH_3COCOOR$; v, AcOH

Scheme 1



Reagents: i, $(COOEt)_2$; ii, CH_3COCH_2COR; iii, AcOH; iv, NaOEt

Scheme 2

Running Title: Tetrazolo[5,1-*f*]-1,2,4-triazine

Graphical Abstract