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Synthesis and Antifungal Activity of Some New Fluorine-Substituted 4-Thiazolidinone Bearing 1,2,4-Triazinone

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Abstract

Fluorine substituted 4-thiazolidinone **5** bearing 1,2,4-triazinone obtained from the condensation of 3-Amino-6(2'-aminophenyl)-1,2,4-triazin-5(4H)-one (**2**) with an aromatic aldehyde followed by cycloaddition with mercaptoacetic acid afforded the thiazolidinone (**4**), and treatment with ethyl trifluoroacetate. Structure of the products has been deduced from their correct elemental analysis and spectral measurements. The antifungal activity of the new fluorinated target also has been evaluated.

Keywords

Synthesis, Fluorine , 4-Thiazolidinone, 1,2,4-Triazin Fungal

1. Introduction

The use of heterocycles as chemical fertilizers to increase the yield of crops and to eliminate all kinds of parasites able to attack the cultivation is becoming more important because of the great problem facing the world to provide food to an increasing population [1]. Among these heterocycles, (2-thioxo-thiazolidin-4-one) and its derivatives exhibit a wide spectrum in the medicinal, pharmacological and agricultural [2], as well as use for determination of Cu(II), Hg(II), Cl^- and CN^- ions in the industrial wastewater [3]. On the other hand, functionally 1,2,4-triazine derivatives have essential properties as medicinal, pharmacological and biological fields [4] [5] [6]. Also, the introduction of fluorine atom to the heterocyclic systems often enhances and improves their properties [7] [8] [9]. Based upon these observations, the present work reports synthesis of some new fluorine-substituted 4-thiazolidinone starting from 3-amino-6-(2'-aminophenyl-1,2,4-

triazin-5(4H)-one (**2**) in view of their antifungal activity.

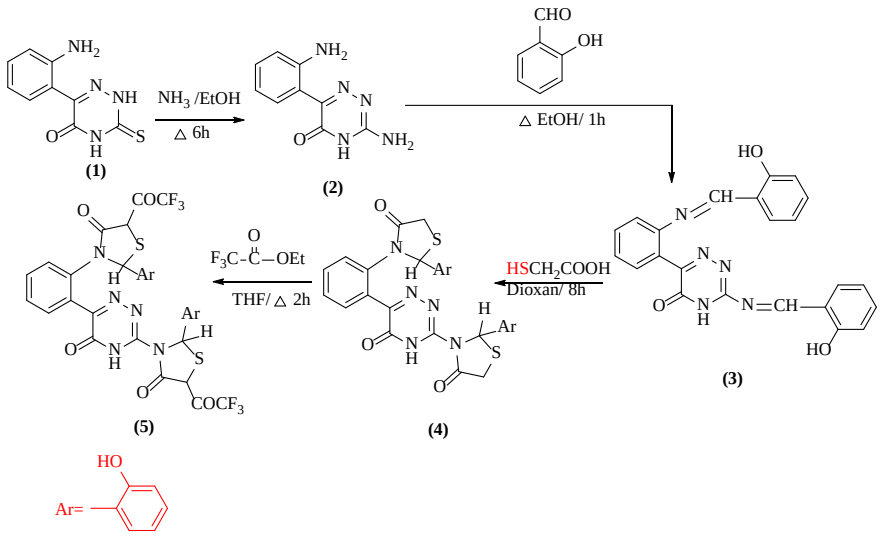
2. Chemistry

3-(Amino)-6-(2′-aminophenyl)-1,2,4-triazin-5(4H)-one (**2**) prepared by aminolysis of 3-mercapto-6-(2'-aminophenyl)-1,2,4-triazin-5(4H)-one (**1**) [10] in reflux ethanol. Condensation of compound **2** with 2-hydroxybenzaldehyde (1:2 by moles) in reflux ethanol yielded the arylidene derivative **3** which underwent cycloaddition with thioglycolic acid in reflux dioxan afforded the 4-thiazolidinone **4**. Fluoroalkylation of compound **4** by reflux with ethyl trifluoroacetate in THF furnished 3-[(4'-oxo-2'-aryl-)-5-(trifluoroacetyl)thiazolidin-3'-yl]-6-[(2'-4"-oxo-2-aryl-5"-trifluoroacetyl)-thiazolidin-3'-yl]phenyl]-1,2.4-triazin-5(4H)-one (**5**) (Scheme 1). Fluoroalkylation of compound **4** takes the place of active methylene ($COCH_2$) rather than of NH proton of 1,2,4-triazinone.

3. Results and Discussion

Former structure of compound **2** deduced from correct elemental and spectral data. The IR absorption spectrum showed ν at 3200, 3100 (NH, NH), 3080 (NH_2), 1670 (C=O) and 1630 (deformation of NH_2) cm^{-1}. The ^{1}HNMR spectrum recorded δ at 13.4, 5.5 and 3.5 ppm attributed to NH (1,2,4-triazine) and two NH_2, with aromatic protons δ 7.68 - 6.9 ppm. The ^{13}C NMR spectrum give us a good indication, that showed δ at 172.95, 147.62, 147.24 ppm for CO and two C-NH_2. Also, δ at 115.48, 114.87 and 114.75 ppm for carbon of 1,2,4-triazine.

IR spectrum of compound **3** recorded a lack both NH_2 functional groups, Also that ^{1}HNMR showed a lack NH_2 protons, with the presence of δ at 8.03, 8.01 ppm for two N=CH protons. On the other hand, ^{1}H NMR spectrum of compound **4** showed a resonated CH_2 protons at δ 2.68 ppm which lack's in its of compound **5**, which confirm that fluoroalkylation lack's place at CH_2 and not NH position. The IR spectrum of **5** showed mainly ν at 1250 cm^{-1} for C-F. The ^{13}CNMR



Scheme 1. Synthesis of compounds **2-5**.

spectrum of **5** exhibited a resonated signal at 149 ppm attribute to C-F carbons atom, with δ at 162, 158 & 152 for 3 C=O and δ at 23 ppm CH aliphatic.

4. Experimental

The melting points determined on Gallen-Kamp melting point apparatus and are uncorrected. The infrared (IR) spectra recorded on Perkin-Elmer model RXI-IR 55529. ^{1}H and ^{13}C NMR spectra recorded on a BurkerDPX-400 FT NMR spectrometer using tetramethylsilane as the standard internal and DMSO-d_6 as solvent (chemical shift in δ, ppm). Spilling patterns designated as follows: s, singlet; d, doublet; m, multiplet. Elemental analysis performed on 2400 Perkin Elmer series 2 analyzer. Direct-MS spectra carried out using quadruple MS (Electronic ionization mod El mode with source temperature: 200˚C) at 70 eV.

4.1. 3-Amino-6-(2'-Aminophenyl)-1,2,4-Triazin-5(4H)-One (2)

To compound **1** (5 gm), liquid ammonia (39%, 50 ml), in abs. EtOH (100 ml), refluxed for 6 h, cooled. The resulted solid, filtered off and crystallized from EtOH to give **2**. Yield 80%, mp: 213˚C - 216˚C. IR (ν) cm^{-1}: 3200, 3100(NH & NH), 3080(NH_2), 3020(Ar-CH), 1670 (C=O), 1630(deformation of NH_2), 820 (*o*-substituted phenyl).^{1}H NMR (DMSO-d_6) δ ppm: 13.4, 5.5 and 3.5 (each s of 3 NH of 1,2,4-triazine), 7.68 - 6.9 (m, 4H, aromatic protons), ^{13}C NMR (DMSO-d_6) δ ppm: 172.95(C=O). 147.62(C=N), 147.24, 145(two C-NH_2), 115.48, 114.87.114.75 (aromatic carbons). Analytical data, Calcd, C, 53.20; H, 4.43; N, 34.48% for $C_9H_9N_5O$ (203). Found: C, 52.98; N, 4.20; N, 4.20; N, 34.13%.

4.2. The Schiff Base 3

A mixture of **2** (0.01 mol) and 2-hydroxybenzaldehyde (0.02 mol) in abs. EtOH (100 ml) refluxed for 1 h, cooled. The yielded solid, filtered off and crystallized from EtOH to give **3**. Yield 81%, mp: 198˚C - 202˚C. IR (ν) cm^{-1}: 3500(OH), 3120(NH), 1610, 1580(C=N), 1660 (C=O), 850 (*o*-substituted phenyl). ^{1}H NMR (DMSO-d_6) δ ppm: 11.55 (*s*, IH, NH of 1,2,4-triazinone), 8.03, 8.01(two N=CH). 7.2 - 6.9, 6.7 - 6.5, 6.4 - 6.11(each *m*, 12H, aromatic protons). Analytical data, Calcd, C, 67.15; H, 4.13; N, 17.03% for $C_{23}H_{17}N_5O_3$. Found: C, 66.89; H, 4.01; N, 16.75%.

4.3. 3-(4-Oxo-Thiazolidin-3'-yl)-6-(2'-(4-Oxo-Thiazolidin-3'-yl) Phenyl-1,2,4-Triazin-5(4H)-One (4)

A mixture of **3**(0.01 mol) and thioglycolic acid (20 ml) in dioxan (100 ml) refluxed for 8h cooled then poured onto ice. The produced solid, filtered off and crystallized from dioxane to give **4**. Yield 70%, m.p: 187˚C - 190˚C. IR (ν) cm^{-1}: 3500 - 3400 (b, OH, OH), 3120 (NH), 3030 (aromatic CH), 2980 (aliphatic CH_2), 1680 - 1660 (C=O), 1380(cyclic NCSC), 1440 (deformation CH_2), 900, 820 (*o*-substituted phenyl). Analytical data, Calcd, C, 57.96; H, 3.75; H, 3.75; N, 12.52; S, 11.44% for $C_{27}H_{21}N_5S_2O_5$(559). Found: C, 57.77; H, 3.55; N, 12.31; S,

10.98%.

4.4. 3-[(4'-Oxo-2'-(2"-Hydroxyphenyl)-5"-(Trifluoroacetylthiazolidin-3'-yl]-6-(2'-(4"-oxo-2"-(2'"-Hydroxyphenyl)-5"-(Trifluoroacetyl)-Thiazolidin-3'-yl) Phenyl-1,2,4-Triazin-5(4H)-One (5)

A mixture of **4** (0.01 mol) and ethyl trifluoroacetate (0.02 mol) in THF (100 ml) refluxed for 1h, cooled then poured on to ice. The resulted solid, filtered off and crystallized from THF to give **5**. Yield 60%, mp: 244˚C - 247˚C. IR (ν) cm^{-1}: 3500 - 3400 (b, OH, OH), 3110 (NH), 3015 (aromatic CH), 2880 (aliphatic CH), 1710, 1700, 1680 (3 C=O), 1660 - 1650 (2 C=O of thiazolidin-4'-one), 1440 (deformation CH), 1350 (cyclic NCSC), 1250 (C-F), 910, 880,820 (*o.* substituted phenyl). ^{1}H NMR (DMSO-d_6) δ ppm: 12.0 (*s*, 1H, NH of triazine), 8.8 - 8.66, 7.12 - 7.00, 6.90 - 6.70 (each *m*, 12H, aromatic H), 4.8 (2H, CH-S of thiazolidinone). ^{12}C NMR(DMSO-d_6) δ ppm: 162(C=O), 158(C=O), 152(C=O), 149(C-F), 142(C=N of 1,2,4-triazine), 132-112 (aromatic carbons), 98 (C-S). Analytical data, Calcd C, 49.53; H, 2.52; N, 9.32; S, 8.52% for $C_{31}H_{19}F_6N_5O_7S_2$ (751): Found C, 49.08; H, 2.32; N, 9.11; S, 8.09 %. M/S(752, M^{+2}, 5%), 141 (100) as $COCSF_3N$ (Figure 1).

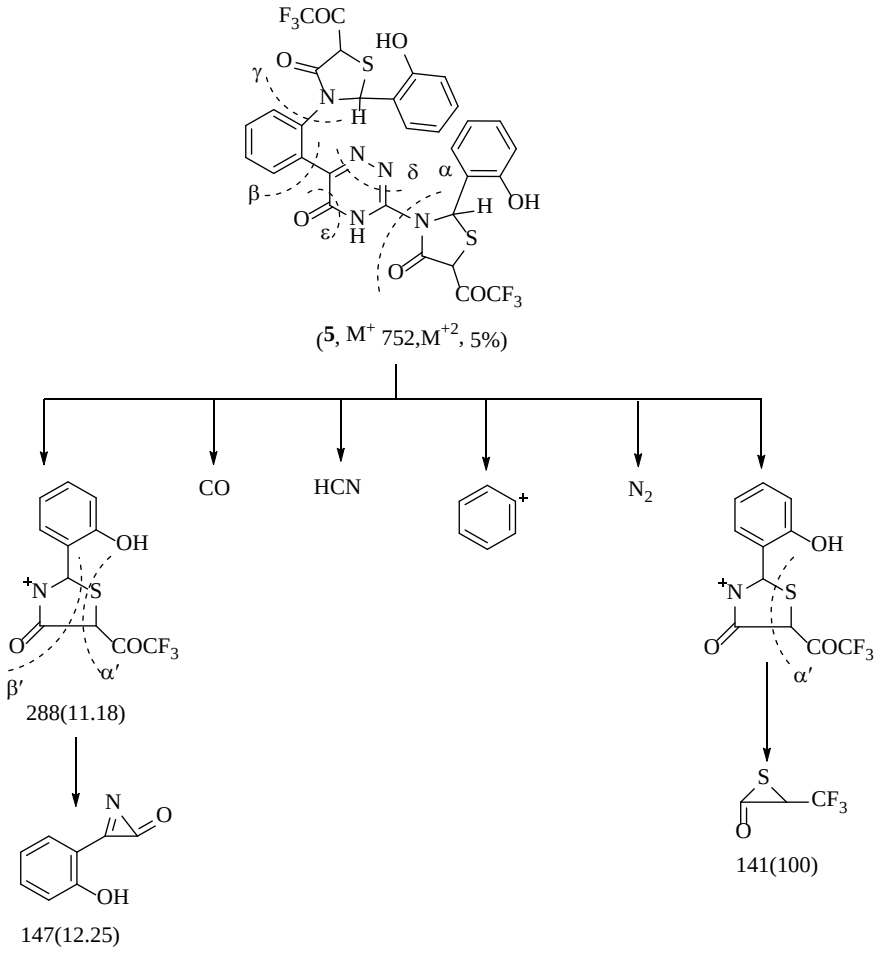


Figure 1. Mass fragmentation pattern of compound **5**.

Table 1. The antifungal activity of the un/fluorinated systems (4 & 5). Control used: DMF (30% germination).

Compound	Concentration μg/mL	% Germination in so if infested with fungi
4	500	65
	1000	70
5	500	78
	1000	80

5. Antifungal Evaluation

Firstly, *in vitro*, the newly prepared compounds were assayed against the growth of some *phytopathogenic* fungi associated with what grains, *i.e. Fusarium moniliforme*. The assay performed by incorporating the tested compounds with nutrient agar at different concentration. The compounds dissolved in DMF and distilled water. The poisoned media were poured into sterile Petri-dishes and allowed to solidify. Each dish inoculated with a 4 mm diameter disk of inoculum removed from a 7 day old culture of the tested pathogens. Other media supplemented with DMF serving as a control. Treatment replicated 3 times, and the plates incubated at 27˚C.

Growth on the compound amended media determined by men swing colony diameter (cm) and growth inhibition calculated with reference to the control. ED_{50} values determined by regression analysis of the long probit transformed data [11] [12]. From the result obtained show that compounds **5** and **4** are the most effective against the tested fungi. A higher effect of these compounds is may be due to containing fluorine atoms and/or 4-thiazolidinone moiety (**Table 1**).

Secondly, *in vivo*, the compound **5** has highest protecting activity on the grains (*Tritium aestivum* C.V Giza lss) of wheat against the fungal infection and increases the wheat germination compared with untreated grains. The best control of the used fungi achieved by 1000 mg/ml of compound **4** (704. Germination).

6. Conclusion

The fluorine substituted 4-thiazolidinone bearing 1,2,4-triazinone synthesized and compared with non-fluorinated were the fluorinated systems 5 exhibits highest germination (more plant protection) than the non-fluorinated systems 4 (lower plant protection).

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