



Synthesis of Fluorine Heterocyclic Nitrogen Systems Derived From Sulfa Drugs as Photochemical Probe Agents for Inhibition of Vitiligo Disease-Part II

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Abstract: Some more new bioactive fluorine heterocyclic systems containing sulfur and nitrogen as six-membered rings such as; *N,N'*-disubstituted-thiobarbituric acid, 3-thioxo-1,2,4-triazino[5,6-*b*]indole, 3-sulfanilamido-1,2,4-triazino[5,6-*b*]indole and 2-trifluoromethyl-4-imino-6-(sulfamido)1,3,5-triazino [3,2-*a*]indole derivatives (**2-13**) have been synthetically derived from the interaction of sulfa drugs with fluorine organic compounds (aldehydes, ketones, anhydride) followed by ring closure reactions. Structures of the targets have been established from their elemental and spectral data. Compounds **3**, **6**, **10** and **13** could be used as photochemical probe agents in compared with nystatin and nalidixic acid for inhibition of vitiligo diseases.

Keywords: Synthetic, Fluoroheterocyclic, Vitiligo, Sulfa-Drugs.

Introduction

In recent years, human pathogenic microorganisms have developed resistance in response to the indiscriminate use of commercial antimicrobial drugs commonly employed in the treatment of infectious diseases¹. In this situation, the undesirable side effect of certain antibiotics and the emergence previously uncommon infections, has forced scientists to look for new antimicrobial substances from various fluorine-heterocyclic systems such as photochemical probe agents.

On the other hand, photodynamic therapy (PDT) is a cancer treatment leading to the selective destruction of malignancies by visible light in the presence of a photosensitizer and oxygen via molecular oxygen into excited triplet state. Activated singlet oxygen or reactive oxygen species play an important role in cytotoxic effects on tumor tissues. Thus, continuing

our interest in the synthesis of biodynamic fluoro-heterocyclic systems for treatment of vitiligo disease. Now we report synthetic six membered rings containing fluorine in view of their biocidal effects as photochemical probe agents for vitiligo inhibition.

Experimental

Melting points were determined using an electrochemical Bibby Stuart Scientific melting point SMP (US) instrument. IR spectra recorded for KBr disc on a Perkin Elmer Spectrum RXI FT-IR system No. 55529. ^1H NMR was recorded for solution in deuterated DMSO with a Bruker NMR advance DPX400 MH using TMS as an internal standard. C-13 spectra were recorded on a VXR-300 (75MHz) Varian spectrometer operating at room temperature. Mass spectra were measured on GCMS-Q 1000-Ex Spectrometer. Electronic absorption spectra were recorded on Shimadzu UV and visible 3101 pc spectrophotometer. Microanalysis (sulfur %) were performed in the Micro-analytical center of Cairo University, Egypt.

Preparation of N,N'-disubstitutedthioruea (1a-c)

A mixture of sulfa drugs, as sulfanilamide, sulfa isoxazole and or sulfapyridine (0.01 mol) in DMF (20 mL) and phenylisothiocyanate (0.01 mol) in dioxan (20 mL) was warmed for 1 h, cooled then poured onto ice. The solid thus obtained was filtered off and crystallized to give the compounds **1(a-c)** (Table 1). **1a**: UV (λ_{max}); 285, 277 nm; IR: 3320(NH₂), 3090(NH), 3020(aromatic CH), 1350(NCSN), 1120(C-S), 850,780 cm^{-1} (substituted phenyl).

Synthesis of 1,3-disubstituted thiobarbituric acid (2a-c)

Equimolar mixture of compounds (**1a-c**) with dimethyl malonate in sodium methoxide solution was refluxed for 4 h, cooled then poured onto ice-HCl. The obtained solid was filtered off and crystallized to give the compounds (**2a-c**) (Table 1). **2c**: UV (λ_{max}); 302 nm; IR: 3100(NHSO₂), 3020, 2980 (aromatic & aliphatic CH), 1670,1650(2 C=O), 1580(C=N), 1480(def. CH₂), 1380,1330 (NCSN, SO₂), 1180(C-S) and 905, 850,700 cm^{-1} (substituted phenyl). ^1H NMR δ : 8.3(1H, NHSO₂-), 8.2(1H, OH), 7.8-7.6, 7.5-7.3 and 7.2-7.0 ppm (*m*, 12H, aromatic and pyridine protons).

Synthesis of 1,3-disubstituted-5-H, 5-trifluoroacetyl-thiobarbituric acid (3)

A mixture of compound **2c** (0.01 mol) and hexafluoroacetic anhydride (0.012 mol) in THF (20 mL) was warmed under reflux for 2 h and cooled. The resultant solid was filtered off and crystallized to give the compound **3** (Table 1). UV(λ_{max}); 307 nm; IR : 3324(NHSO₂), 3052, 2807 (aromatic & aliphatic CH), 1675(C=O), 1495(def. CH₂), 1358(NCSN), 1129(C-S), 771,719 cm^{-1} (substituted phenyl).

^1H NMR δ : 8.3(1H, NHSO₂-), 8.2(1H, OH), 7.8-7.6, 7.5-7.3 and 7.2-7.0 ppm (*m*, 12H, aromatic and pyridine protons). M/S: *m/z* (Int. %) 548(1), 470(4), 315(2), 232(12), 219(4), 200(22), 185(95), 157(36), 148(18), 129(100).

Preparation of 5-fluoroisatin-3-thiosemicarbazone(4)

A mixture of 5-fluoroisatin (0.01 mol) in ethanol (20 mL) and thiosemicarbazide (0.01 mol, in hot water, 10 mL) was heated for 30 min and cooled. Formed solid was filtered off and crystallized to give the compound **4** (Table 1). IR: 3200, 3150(NH₂, NH) 3010 (aromatic CH), 1640(CONH), 1610 (def. NH₂), 1580(C=N), 1380(NCSN), 1200 (C-S), 780 (substituted phenyl), 660 cm^{-1} (C-F).

Synthesis of 3-mercaptop-8-fluoro-1,2,4-triazino[5,6-b]indole (5)

Thiosemicarbazone, **4** (0.01 mol) and anhydrous K₂CO₃ (10 g) in abs. ethanol (100 mL) was refluxed for 4 h, cooled then poured onto ice-acetic acid. The obtained solid was filtered off and crystallized to give the compound **5** (Table 1).

Preparation of 3-(benzoylsulfanoylphenyl-4-amino)-8-fluoro-1,2,4-triazino[5,6-b]indole(6)

Equimolar amounts of compound **5** and sulfabenzamide in DMF (20 mL) was refluxed for 4 h, cooled and poured onto ice. The solid thus obtained was filtered off and crystallized to give the compound **6** (Table 1). UV(λ_{\max}): 371 nm; IR : 3380(NHSO₂), 3350(NH of Indole), 1650(CONH), 1590(C=N), 1380(NCSN), 720,690 (substituted phenyl), 650 cm⁻¹(C-F); M/S: *m/z* (Int. %) 462(5), 210(100), 184(4), 168(22), 161(9), 134(29), 120(1), 105(14), 77(5).

Preparation of N⁴-arylthiosemicarbazide(7)

A mixture of sulfanilamide (0.01 mol) in DMF (20 mL) and CS₂ (0.015 mol) in THF (20 mL) was added drop wise then warmed on water bath for 1 h. To reaction mixture, hydrazine hydrate (0.01 mol) was added then refluxed for 4 h. The obtained solid after cooling was filtered off and crystallized to give the compound **7** (Table 1).

Preparation of isatin-3-thiosemicarbazone(8)

A mixture of **7** (0.01 mol) and isatin (0.01 mol) in methanol (20 mL) was heated for 1 h then cooled. The obtained solid was filtered off and crystallized to give the compound **8** (Table 1).

3-Arylamino-1,2,4-triazinon[5,6-b]indole(9)

A mixture of **8** (0.01 mol) and ammonium acetate (2 g) with a few drops of glacial acetic acid, was fused at 120-150 °C for 2 h, cooled then treated with methanol. The resulted solid was filtered off and crystallized to give the compound **9** (Table 1). IR:3350(NH₂SO₂), 1710, 1680 (2 COCF₃), 820,750,650 cm⁻¹ (substituted phenyl).

Synthesis of 3-trifluoroacetylaminoaryl-5-trifluoroacetyl-1,2,4-triazino[5,6-b]indole(10)

A mixture of **9** (0.01 mol) and trifluoroacetic anhydride (0.04 mol) in THF (50 mL) was refluxed for 4 h and cooled. The obtained solid was crystallized to give the compound **10** (Table 1). IR: 3350 (NHSO₂), 3100, 3080(NH, NH), 1580(C=N), 1320,1250 (asym. & sym. S=O), 710,690 (substituted phenyl), 650 cm⁻¹(C-F). H¹ NMR δ :8.5(2H, NH₂SO₂-),8.1-7.7, 7.3-7.1 ppm.(each *m*, 4H, 4H of indole and aromatic protons).

Preparation of isatin-3-imino aryl derivative(11)

A mixture of isatin (0.01 mol) and sulfa isoxazole(0.01 mol) in DMF (20 mL) was refluxed for 1 h, cooled then poured onto ice. The produced solid was filtered off and crystallized to give the compound **11** (Table 1).

Fluorination of (11) and formation of 1-trifluoroacetyl-isatin-3-iminoaryl(12)

A mixture of **11** (0.01 mol) and hexafluoroacetic anhydride (0.012 mol) in THF (20 mL) was warmed for 1h and cooled. The produced solid was filtered off and crystallized to give the compound **12** (Table 1). IR: 3300(NHSO₂), 3010 (aromatic CH), 1710, 1680(2C=O), 1580(C=N), 810, 780 (substituted phenyl), 670 cm⁻¹ (C-F).

Synthesis of 1,3,5-triazinoindole derivative(13)

Equimolar mixture of compound **12** and guanidine hydrochloride in DMF (20 mL) was refluxed for 2 h, cooled and poured onto ice. The obtained solid was filtered off and crystallized to give the compound **13** (Table 1). IR: 3337(NHSO₂), 3190(=NH), 3060(aromatic CH), 1673 (exo >CH=NH), 1610, 1580(C=N), 862,796 (substituted phenyl), 1390 cm⁻¹(CF₃). H¹ NMR δ :3.5(1H, NH=C-), 4.2(*m*,2H,-CH=CH- of isoxazole), 8.2(1H, NHSO₂), 7.3, 6.9(2H, benzoprotons) 7.5, 7.7 ppm (2H, aryl protons). M/S: *m/z* (Int. %): 524(20), 340(38), 264(18), 251(22), 213(40),

109(100). ^{13}C NMR: δ 163 (endo C=NH of 1,3,5-triazino), 164 (exo C=N of 3-position of indole), 119.1 (C of CF_3), 154.6 (exo C=N of 2-position of indole), 112.4, 130, 118.8, 131.8, 124.3 (6C of benzopyrol), 156 (=N-C, of aryl SO_2), 138 ($\text{SO}_2\text{-C}_4$ of aryl SO_2), 122, 122, 128.6, 128.6 (C_2 , C_3 , C_5 and C_6 of aryl SO_2), 150.6 (NH-C of isoxazole), 127 (N-C), and 138 ppm (O-C) of isoxazole moiety.

Table 1. Physical properties of new fluorine heterocyclic systems (**1-13**)

Comp. No.	m.p. $^{\circ}\text{C}$	Yield, %	Solvent of cryst.	Molecular formula	S analysis % *	
					Found	Calc.
1a	200	70	Dioxan	$\text{C}_{13}\text{H}_{13}\text{N}_4\text{S}_2\text{O}_2$	19.79	20.84
1b	166	78	Dioxan	$\text{C}_{16}\text{H}_{13}\text{N}_4\text{S}_2\text{O}_3$	16.42	17.11
1c	170	75	Dioxan	$\text{C}_{18}\text{H}_{15}\text{N}_4\text{S}_2\text{O}_2$	15.82	16.62
2a	180	80	MeOH	$\text{C}_{16}\text{H}_{13}\text{N}_3\text{S}_2\text{O}_4$	16.03	17.00
2b	160	72	MeOH	$\text{C}_{19}\text{H}_{14}\text{N}_4\text{S}_2\text{O}_5$	13.74	14.47
2c	120	70	MeOH	$\text{C}_{21}\text{H}_{16}\text{N}_4\text{S}_2\text{O}_4$	13.44	14.15
3	78	74	THF	$\text{C}_{23}\text{H}_{15}\text{N}_4\text{F}_3\text{S}_2\text{O}_5$	16.37	16.55
4	342	60	EtOH	$\text{C}_9\text{H}_7\text{N}_4\text{FSO}$	12.63	13.44
5	>360	65	EtOH	$\text{C}_9\text{H}_5\text{N}_4\text{FS}$	13.81	14.54
6	340	80	DMF	$\text{C}_{22}\text{H}_{15}\text{N}_6\text{FSO}_3$	6.50	6.92
7	200	60	EtOH	$\text{C}_7\text{H}_{10}\text{N}_4\text{S}_2\text{O}_2$	25.51	26.01
8	285	65	DMF	$\text{C}_{15}\text{H}_{13}\text{N}_2\text{S}_2\text{O}_3$	16.85	17.06
9	302	70	DMF	$\text{C}_{15}\text{H}_{12}\text{N}_6\text{SO}_2$	8.88	9.41
10	320	80	DMF	$\text{C}_{19}\text{H}_{10}\text{N}_6\text{F}_6\text{SO}_4$	5.34	6.01
11	160	70	DMF	$\text{C}_{17}\text{H}_{12}\text{N}_4\text{SO}_4$	8.08	8.69
12	208	70	THF	$\text{C}_{19}\text{H}_{11}\text{N}_4\text{F}_3\text{SO}_5$	6.54	6.90
13	168	80	DMF	$\text{C}_{20}\text{H}_{12}\text{N}_7\text{F}_3\text{SO}_3$	6.60	6.57

*All the compounds give satisfactory sulfur analysis

Results and Discussion

Wenyan *et al.*² reported a facile synthesis of novel-fluorine containing pyrido[4,3-b]pyrimidines as herbicidal agents against the roots of rape and barnyard grass. Also, thiobarbituric with incorporation of sulfa drugs enhanced their biocidal effects³. Thus, addition of phenyl isothiocyanate to some sulfa drugs such as sulfanilamide, sulfa isoxazole and sulfapyridine in warming DMF yielded *N,N'*-disubstituted thiourea (**1a-c**) which upon heterocyclization via refluxing with dimethyl malonate in sodium methoxide led to the direct formation of 1-phenyl-3-sulfanilamido thiobarbituric acid (**2a-c**). Fluorination of **2c** by refluxing with hexafluor acetic anhydride in THF produced the compound 1,3-disubstituted-5-trifluoroacetyl thiobarbituric acid (**3**) [Scheme I]. Structures of **1-3** have been deduced (Figure 1) from elemental and spectral data. M/S of **3c** recorded m/z (Int.%) 548(M^+ ,I), with a base peak at 129(100).

Indole-2,3-dione has become of increasing important in recent years owing to its pharmacological properties, for which it have been used as starting material for building various heterocyclic systems^{4,5}. Abdel-Rahman⁶⁻⁹ prepared a large number of fluoroindolotriazines as anti-cancer and anti-HIV agents.

Thus, condensation of 5-fluoroisatin with thiosemicarbazide in hot ethanol-acetic acid produced (Scheme 2) thiosemicarbazone (**4**) which upon heterocyclization by refluxing with aqueous K_2CO_3 yielded 3-thioxo-8-fluoro-2H,5H-1,2,4-triazino[5,6-b]indole (**5**). Amination of **5** via a simple nucleophilic attack of sulfabenzamide in boiling DMF furnished 3-aryl-amino-8-fluoro-5H-1,2,4-triazino[5,6-b]indole (**6**). Former structures of **4-6** (Figure 2) have been established from their elemental and spectral data. M/S of **6** showed m/z (Int. %) 462(M^+ ,5) with a base peak of m/z 210(100).

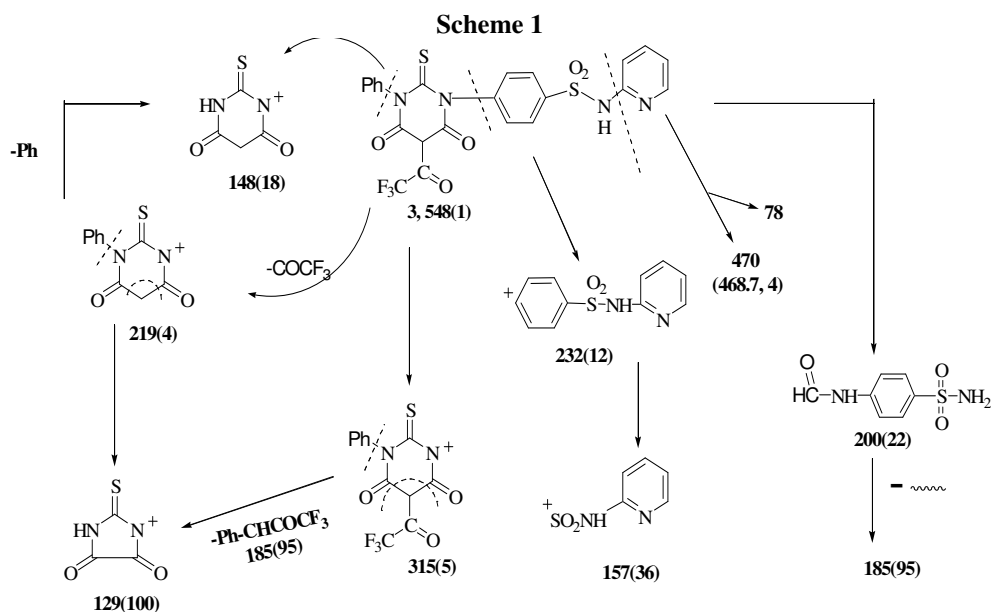
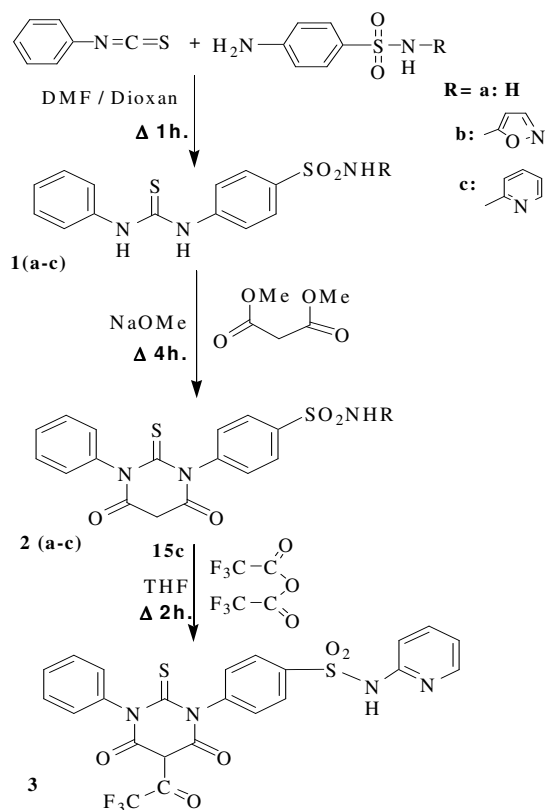


Figure 1. Mass fragmentation pattern of compound 3

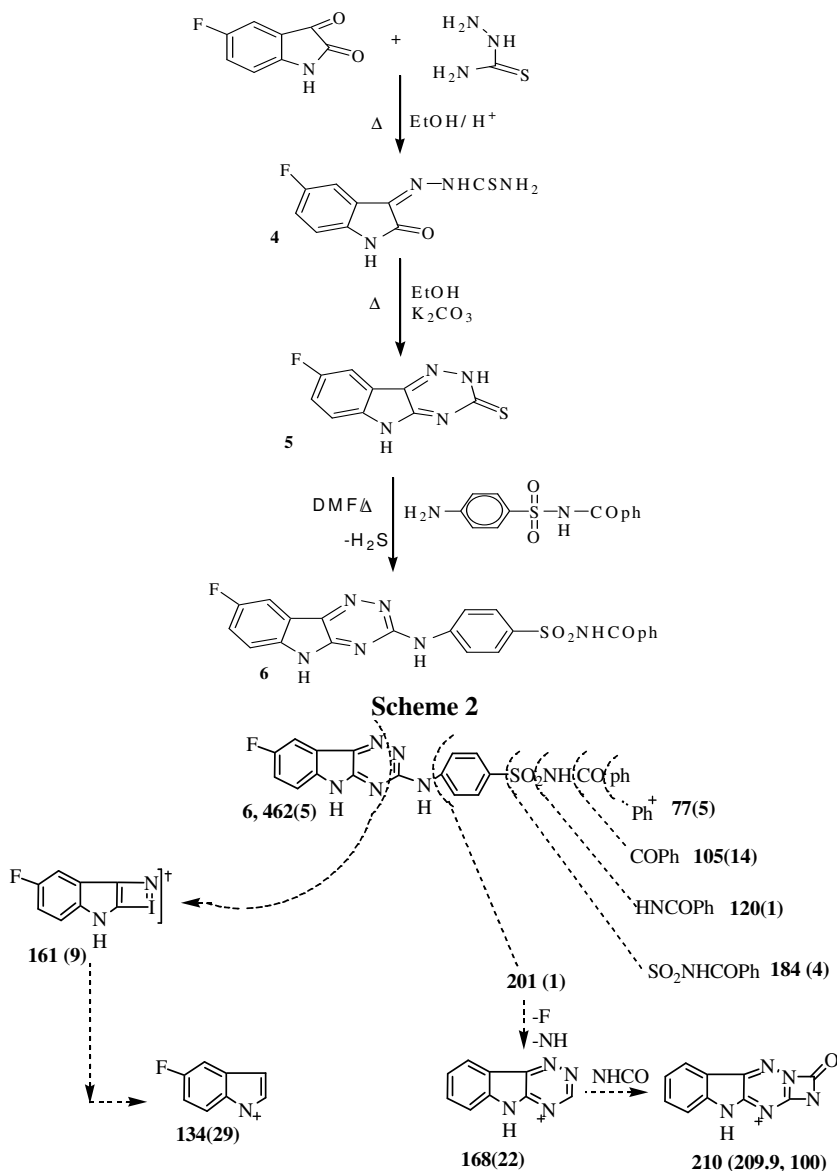
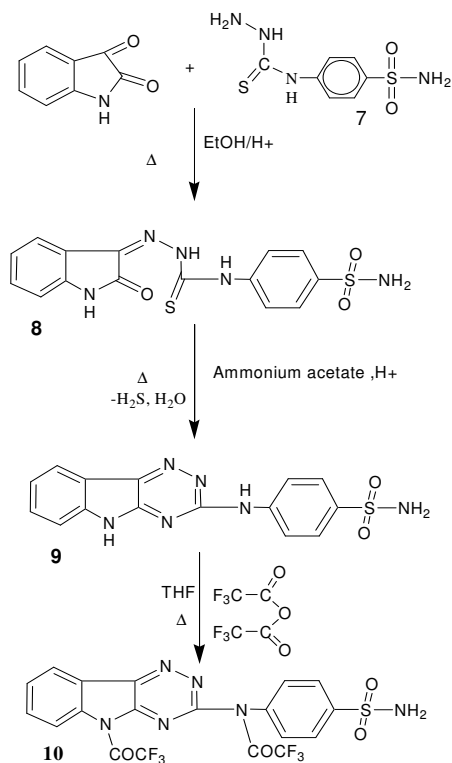


Figure 2. Mass fragmentation pattern of compound 6

Abdel-Rahman *et al.*¹⁰⁻¹³ prepared a large number of triazinoindole derivatives as biocidal effects. In view of the above applications the synthesis and characterization of some more triazinoindoles, as a part of our extensive research program to rapidly synthesize novel 3-(*N*-trifluoroacetyl sulfamido)-5-trifluoro-1,2,4-triazino[5,6-*b*]indole(**10**) was deduced from condensation of the *N*^f-aryl-thiosemicarbazide (**7**) with isatin in boiling DMF to give thiosemicazone (**8**), which upon heterocyclization by refluxing with ammonium acetate-acetic acid produce (**9**). Fluorination of **9** by refluxing with hexafluoro acetic anhydride in THF yielded **10** (Scheme 3).



A variety of attractive pharmacological effects were attributed to the fluorinated mono- and polycyclic-1,3,5-triazines by Anton *et al.*¹⁴, were synthesized new fluorinated triazolo-1,3,5-triazine derivatives and lack of inhibitory activity against bovine dihydrofolate reductase realized via other mechanisms.

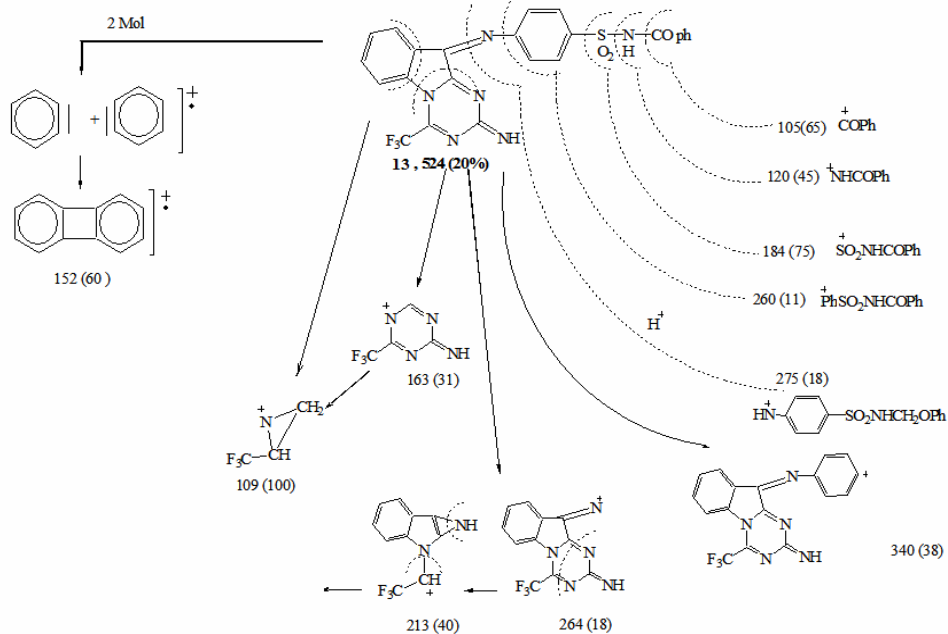
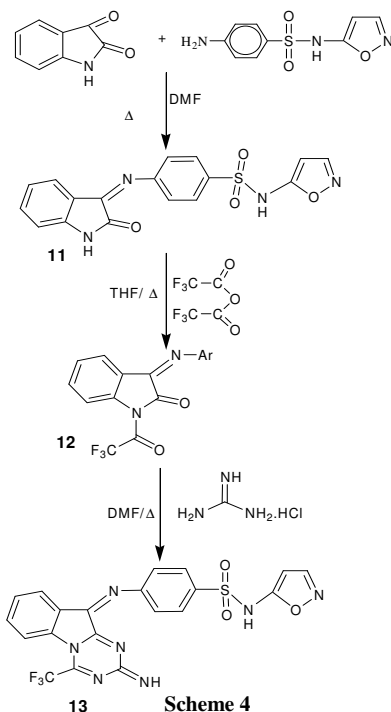
Thus, condensation of isatin with sulfa isoxazole in boiling DMF produced 3-iminoisatin (**11**) which underwent fluorination by warming with hexafluoroacetic anhydride in THF afforded *N*-trifluoroacetyl-3-iminoisatin (**12**). Heterocyclization of **12** via refluxing with guanidine in sodium ethoxide furnished 2-trifluoro methyl-4-imino-6-(sulfamido-1-yl)-1,3,5-triazino[3,2-*a*]indole(**13**) [Scheme 4]. Former structure of **13**, it was confirmed from elemental and spectral data. M/S recorded m/z (Int. %) 524(M^+ , 20), with a base peak of m/z 109(100) [Figure 3].

Biocidal effects

Evaluation of the synthesized compounds against microorganisms which caused diseases by using photodynamic therapy (PDT)¹⁵ through activated singlet oxygen or reactive oxygen species (ROS). PDT can be applied as an effective cancer treatment due to enhanced permeability and retention (EPR) effect in tumors in comparison with normal tissues and is easily controlled by limiting the area of light irradiation^{16,17}.

Antimicrobial assays

The synthesized compounds were tested *in vitro* using the agar diffusion disc method^{18,19} against gram negative bacteria *E. coli*, *P.aeruginosa* and *K. pneumonia* and gram positive bacteria *B. subtilis*, *S.aureus* and fungi *A. fumigates*, *C. albicans*.



Antimicrobial potentialities of the tested compounds were estimated by placing prestilized filter paper disks (6 mm in diameter) impregnated with 50 $\mu\text{g}/\text{disk}$. DMF, which showed no inhibition zones, was used as a solvent. Inhibition zones (IZ) of the tested compounds (mm)

were measured after 24-28 h incubation period 37 °C for bacteria and after 5 days incubation period at 28 °C for fungi (Table 2). The minimal inhibitory concentration (MIC) method of the biologically active compounds was applied using different concentrations per disk against bacteria and fungi using nalidixic acid and nystatin as reference drugs (Tables 3 & 4).

Table 2. The Preliminary screening of antimicrobial activity of the synthesized compounds

Compd. No.	Microorganisms / Inhibition Zone mm						
	Gram +ve bacteria		Gram +ve bacteria			Fungi	
	<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.aeuruginosa</i>	<i>K.pneumonia</i>	<i>C.albicans</i>	<i>A.fumigates</i>
3	16	20	13	18	16	9	6
6	16	24	13	18	16	8	6
10	16	26	13	20	16	10	6
13	16	24	13	18	16	8	6
<i>Na.*</i>	32	30	30	12	22	6	6
<i>Ny.*</i>	6	6	6	6	10	10	32

**Na:* Nalidixic acid, 30 µg/disk, Bioanalyze, Egypt.

**Ny:* Nystatin, manufactured by Pasteur Lab., Egypt, NS 100 units.

The sensitivity of microorganisms of the compounds is defined in the following manners:

Highly active: inhibition zone ≥ 12 mm

Moderately active: inhibition zone 9- 12 mm

Slightly active: inhibition zone 6-9 mm

Not sensitive: inhibition zone 6 mm

Table 3. MIC of the biological active compounds towards the gram positive bacteria* :

Compd. No.	Inhibition zones, mm									
	<i>B. subtilis</i>					<i>S. aureus</i>				
	50	40	30	20	10	50	40	30	20	10
3	16	16	12	9	6	20	13	10	8	6
6	16	10	8	6	6	24	15	10	8	6
10	16	16	12	10	6	26	24	12	10	6
13	16	12	10	8	6	24	20	10	8	6

* Concentration in µg / disk

Table 4. MIC of the biological active compounds towards gram negative bacteria

Compd. No.	Inhibition zones, mm														
	<i>E. coli</i>					<i>P. aeuruginosa</i>					<i>K.pneumonia</i>				
	50	40	30	20	10	50	40	30	20	10	50	40	30	20	10
3	13	13	10	8	6	18	15	10	8	6	16	11	10	8	6
6	13	11	11	8	6	18	13	9	8	6	16	11	10	8	6
10	13	12	11	8	6	20	16	10	8	6	16	11	10	8	6
13	13	11	11	8	6	18	13	9	8	6	16	11	10	8	6

Antimicrobial assay using UV (366 nm) light

This test was performed as mentioned before but the Petri-disks containing microorganisms and the testing compounds were subjected to UV light (366 nm) for 3 h before transferred to the incubation periods (Table 5). The obtained results of the antimicrobial tests against the fluorinated heterocyclic systems indicated that:

- All the tested compounds were more highly active toward all tested microorganisms, in compare with nystatin antibiotic.
- Also, MIC of tested compounds showed activities more than nystatin, especially towards *B.subtillis*, *S.aureus*, *E.coli*, *P.aeuroginosa* and *K.pneumonia*.

iii) After using UV-visible light, the tested compounds showed an additional activity especially towards *B. subtilis*, *P.aeuroginosa* and *C.albicans*.

Table 5. Preliminary screening using UV (366 nm) light*

Compd. No.	Microorganisms, Inhibition zones in mm						
	Gram +ve bacteria		Gram -ve bacteria		Fungi		
	<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.aeuruginosa</i>	<i>K.pneumonia</i>	<i>C.albicans</i>	<i>A.fumigates</i>
3	20			20		10	
6	20	No change		20	No change	10	No change
10	20			22		12	
13	20			20		10	

*Increasing in activity by using UV light (366 nm)

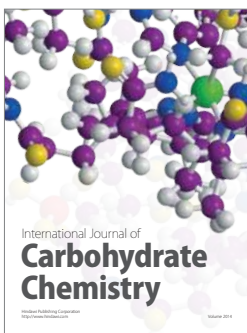
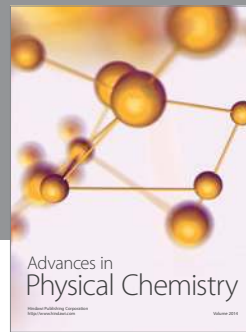
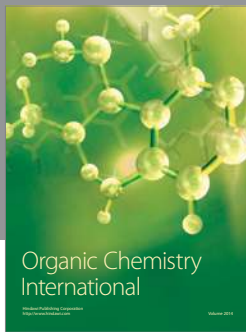
A higher biocidal and photochemical probe of all synthesized compounds, mainly due to connection of fluorine atom or CF₃ and COCF₃ groups at the ends of nitrogen heterocyclic systems as acceptor-donor causing a type of biodynamic electron-motion which led to more effects towards treatment of vitiligo.

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