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The 2-(1-methylhydrazino)quinoxaline 4-oxides **9a,b** were converted into the pyridazino[3,4-*b*]-quinoxalines **10a,b,15a,b,22** and 1,2-diazepino[3,4-*b*]quinoxalines **29a-c**, which were further transformed into the 3-substituted 1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **5-8**.

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Introduction.

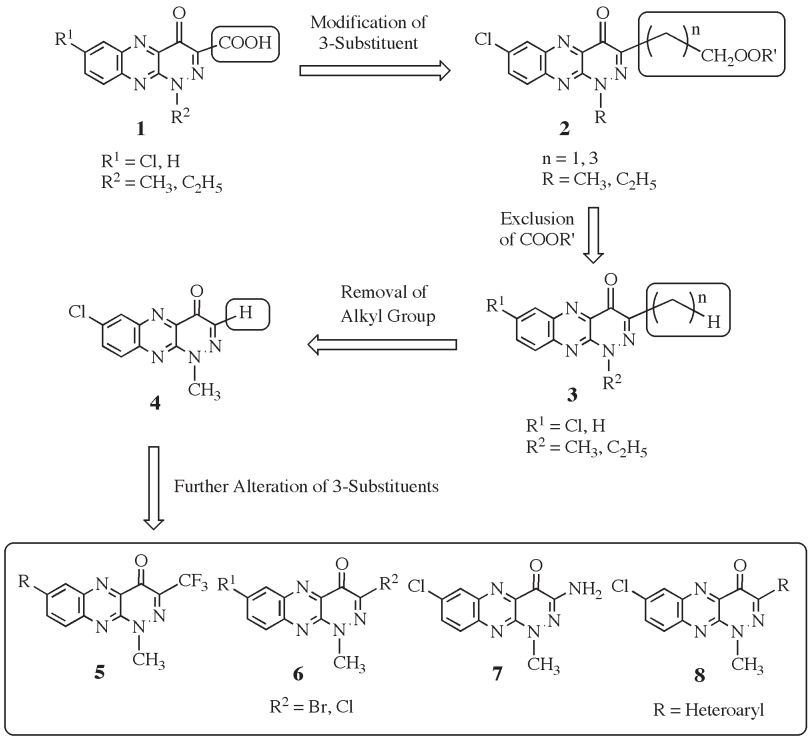
In the 6th and 7th International Symposium on the Chemistry and Pharmacology of Pyridazines (ISCPP), we have presented the synthesis of the 1-alkylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **1-4** [1-4] as candidates of antibacterial quinolone analogues (Scheme 1). From our screening data, compounds **1** were not so potent to some bacteria [1], and hence we undertook the modification for the 3-substituent of compounds **1**. The 3-substituent modification is shown in Scheme 1. At first, the methylene group insertion was carried out between the heterocyclic nucleus and the carboxyl group to produce compounds **2** [2]. Subsequently, the carboxyl group was excluded to provide compounds **3** [3]. Then, the removal of the 3-alkyl group furnished compound **4** [4]. Compounds **2** had weak antibacterial activities [2], but compounds **3** [3] and **4** [4] possessing no carboxyl group at the 3-position showed good antibacterial activities and antifungal activities as described later in the section of screening data. Thus, we further planed the synthesis of various 1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones without the carboxyl group at the 3-position in order to search for more potent compounds. In the present symposium, 9th ISCPP, we will present the synthesis of the 1-methylpyridazino[3,4-*b*]-quinoxalin-4(1*H*)-ones **5-8** (Scheme 1) [5-8] and the biological activities for compounds **3-6**.

Synthesis of 1-Methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones.

1. 3-Trifluoromethyl Quinolone Derivatives **5** [5].

The reaction of the 2-(1-methylhydrazino)quinoxaline 4-oxides **9a,b** with ethyl trifluoroacetoacetate gave the 1,5-

Scheme 1

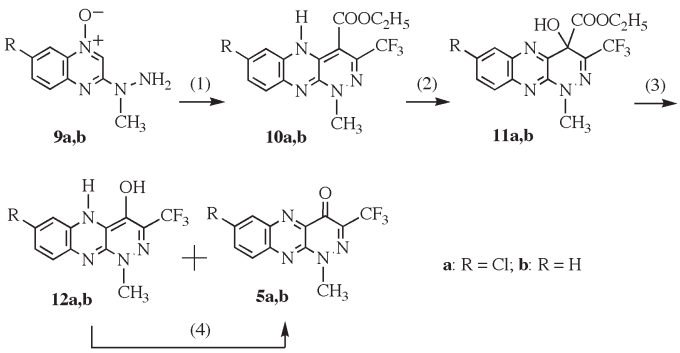


dihydro-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates **10a,b**, respectively (Scheme 2), presumably *via* intermediates **A-C** (Chart 1) [5] in a process as follows; the initial dehydration to a hydrazone intermediate **A**, cyclization to an intermediate **B**, dehydration to an intermediate **C**, and then prototropy to compounds **10a,b**. A mechanism *via* an adduct intermediate **D** would not be favored, since the reaction of 6-chloro-2-hydrazinoquinoxaline 4-oxide **13** with acetylacetone provided the 6-chloro-2-(3,5-dimethylpyrazol-1-yl)quinoxaline 4-oxide **14** presumably *via* an intermediate **E** (Scheme 3) [9]. The oxidation of compounds **10a,b** with nitrous acid afforded the 1,4-dihydro-4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxaline-4-carboxylates **11a,b**, whose reaction with 1,8-diazabicyclo[5.4.0]-7-undecene produced the 1,5-dihydro-4-hydroxy-3-trifluoromethylpyridazino[3,4-*b*]quinoxalines **12a,b** and/or 3-trifluoromethyl quinolone analogues **5a,b**, respectively (Table 1). The oxidation of compounds **12a,b** with sodium bromate gave the 3-trifluoromethyl quinolone analogues **5a,b**, respectively.

Table 1
Yields of Compounds **12a,b** and **5ab**.

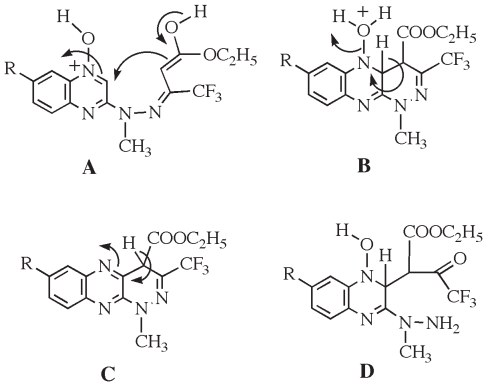
Compound	Product (Yield %)	
11a	**12a** (90)	**5a** (0)
11b	**12b** (74)	**5b** (20)
12a		**5a** (84)
12b		**5b** (87)

Scheme 2



Reagents: (1) Ethyl trifluoroacetoacetate, p-Toluenesulfonic acid monohydrate in Dioxane; (2) $NaNO_2$ in H_2O/Acetic acid; (3) 1,8-Diazabicyclo[5.4.0]-7-undecene in Ethanol; (4) $NaBrO_3$ in H_2O/Acetic acid

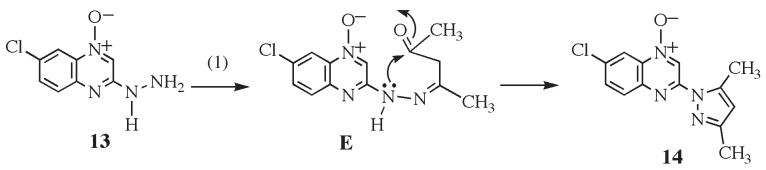
Chart 1



2. 3-Halogeno Quinolone Derivatives **6** [6].

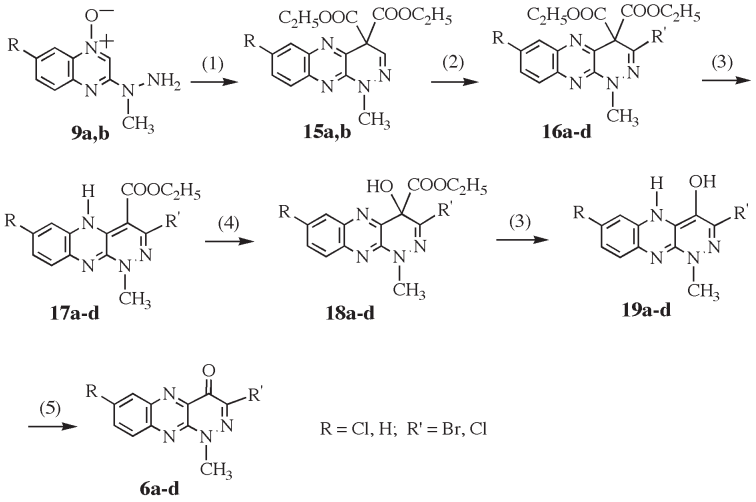
The reaction of the quinoxaline 4-oxides **9a,b** with diethyl ethoxymethylenemalonate gave the 1,4-dihydropyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylates **15a,b**, respectively (Scheme 4), presumably *via* intermediates **F** and **G** (Chart 2) [6] involving the cyclization of an intermediate **F** and then dehydration of an intermediate **G**. Since the pyridazine ring of compounds **15a,b** includes a hydrazone moiety (**H** and **I** in Chart 2) [10,11], the reaction of compounds **15a,b** with bromine, *N*-bromosuccinimide, or *N*-chlorosuccinimide afforded the 3-halogeno-1,4-dihydropyridazino[3,4-*b*]quinoxaline-4,4-dicarboxylates **16a-d**, whose reaction with hydrazine hydrate effected the hydrolysis and decarboxylation to provide the 3-halogeno-1,5-dihydropyridazino[3,4-*b*]quinoxaline-4-carboxylates **17a-d**, respectively. The oxidation of compounds **17a-d** with nitrous acid produced the 3-halogeno-1,4-dihydro-4-hydroxypyridazino[3,4-*b*]-quinoxaline-4-carboxylates **18a-d**, whose reaction with hydrazine hydrate resulted in hydrolysis and decarboxylation to give the 3-halogeno-1,5-dihydropyridazino[3,4-*b*]quinoxalin-4-ols **19a-d**, respectively. The oxidation of **19a-d** with *N*-chlorosuccinimide or *N*-bromosuccinimide in water/acetic acid afforded the 3-halogeno quinolone analogues **6a-d**, respectively.

Scheme 3



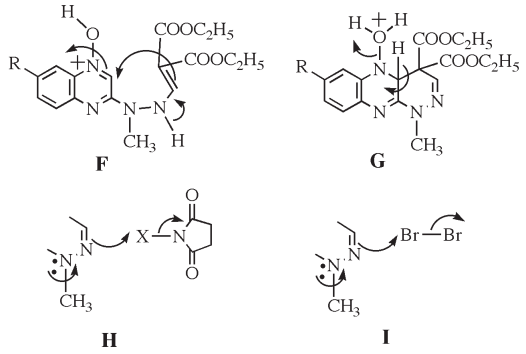
Reagent: (1) Acetylacetone in Ethanol

Scheme 4



Reagents : (1) Diethyl ethoxymethylenemalonate in Acetic acid;(2) Br_2, *N*-Bromosuccinimide, or *N*-Chlorosuccinimide in Acetic acid; (3) Hydrazine hydrate in Ethanol; (4) $NaNO_2$ in H_2O/Acetic acid; (5) *N*-Bromosuccinimide or *N*-Chlorosuccinimide in H_2O/Acetic acid

Chart 2

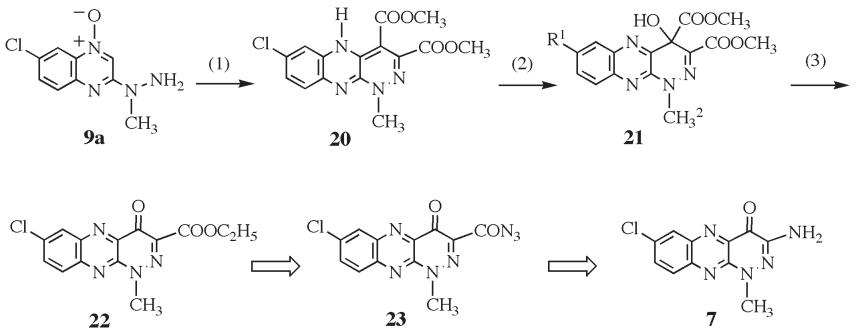


3. 3-Amino Quinolone Derivative **7** [7]

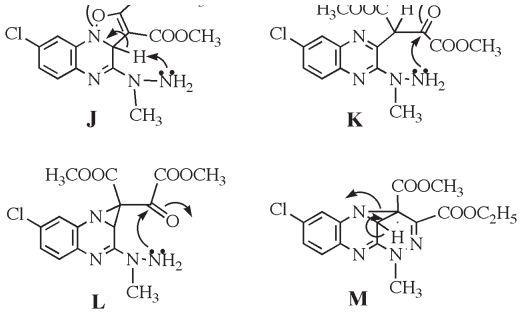
The 3-amino quinolone analogue **7** was synthesized from the 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxylate **22** *via* the 1,4-dihydro-4-oxopyridazino[3,4-*b*]quinoxaline-3-carboxazide **23** (Scheme 5) [7]. Compound **22** was obtained from the quinoxaline 4-oxide **9a** *via* the 1,5-dihydropyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate **20** and 1,4-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxaline-3,4-dicarboxylate **21** [1]. Chart 3 exhibits intermediates **J**-**M** in the conversion of the quinoxaline 4-oxide **9a** to compound **20** [12,13]. Namely, the initial 1,3-dipolar cycloaddition reaction giving an isoxazolo intermediate **J**, ring opening to an intermediate **K**, and then dehydration would afford compound **20**. The other plausible mechanism would be a route *via* the isomerization of an isoxazolo intermediate **J** to an aziridino intermediate **L**, dehydration of an intermediate **L** to an intermediate **M**, and then aziridine ring opening of an intermediate **M** to compound **20**.

The reaction of compound **22** with hydrazine hydrate (13-fold molar amount) gave the 1,5-dihydro-4-hydroxypyridazino[3,4-*b*]quinoxaline-3-carbohydrazide **24** presumably *via* intermediates **N** and **O**, *via* intermediates **P** and **Q**, or *via* intermediates **N** and **Q** (Scheme 6), wherein

Scheme 5



Reagents: (1) Dimethyl acetylenedicarboxylate in Ethanol; (2) $NaNO_2$ in H_2O/Acetic acid;(3) 1,8-Diazabicyclo[5.4.0]-7-undecene in Ethanol

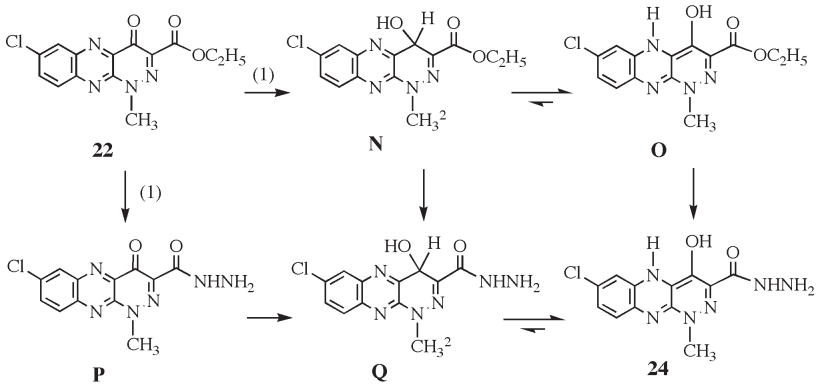


hydrazine would reduce the 4-keto group of compound **22**.

The reaction of compound **24** with aldehydes under reflux in *N*,*N*-dimethylformamide afforded the quinolone analogues **25a-d** accompanied with autoxidation, while heating of compound **24** in dimethyl sulfoxide provided the 2*H*-pyrazolo[3',4':5,6]pyridazino[3,4-*b*]quinoxalin-3(5*H*)-one **26** presumably *via* intermediate **R** (Scheme 7).

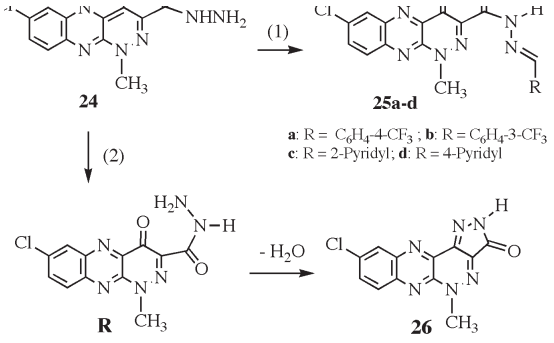
The reaction of compound **24** with nitrous acid produced the 1,4-dihydropyridazino[3,4-*b*]quinoxaline-3-carboxazide **23**, whose heating in triethylamine/water/*N*,*N*-dimethyl-

Scheme 6



Reagent: (1) Hydrazine hydrate (13-fold molar) in Dioxane

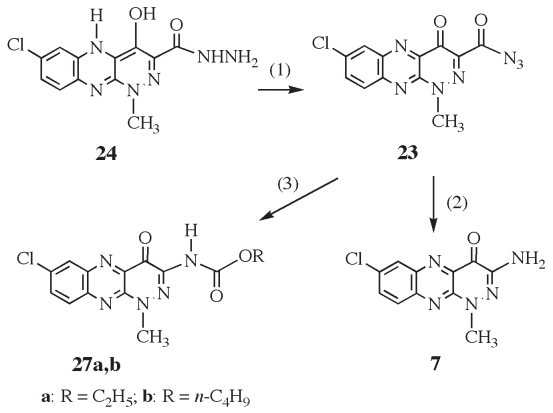
Scheme 7



Reagents: (1) R-CHO in *N,N*-Dimethylformamide; (2) Heat in Dimethyl sulfoxide at 140-160°

formamide gave the 3-amino quinolone analogue **7** (Scheme 8). Heating of compound **23** in triethylamine/ alcohols afforded the 3-carbamate quinolone analogues **27a,b**.

Scheme 8

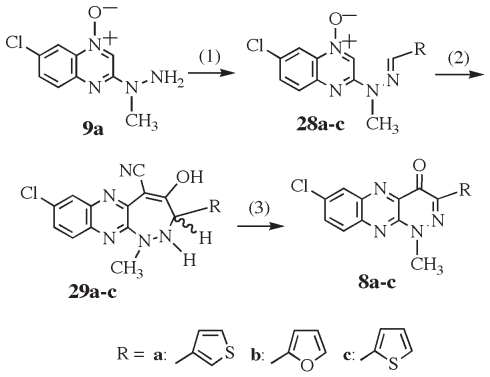


Reagents : (1) $NaNO_2$ in H_2O/Acetic acid; (2) $N(C_2H_5)_3$, H_2O in *N,N*-Dimethylformamide; (3) $N(C_2H_5)_3$ in ROH

4. 3-Heteroaryl Quinolone Derivatives **8** [8].

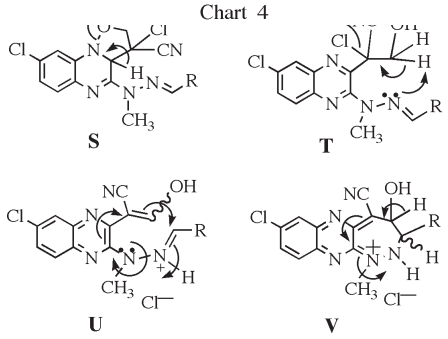
The reaction of the quinoxaline 4-oxide **9a** with thiophene-3-carbaldehyde, furfural, and thiophene-2-carbaldehyde gave the hydrazones **28a-c**, whose reaction with 2-chloroacrylonitrile afforded the 1,2-diazepino[3,4-*b*]-quinoxalines **29a-c**, respectively (Scheme 9) [8], presumably *via* intermediates **S**-**V** (Chart 4) [14,15] in a successive order as follows; the initial 1,3-dipolar cycloaddition reaction providing an intermediate **S**, ring opening to an intermediate **T**, elimination of hydrogen chloride to an intermediate **U**, recyclization to an intermediate **V**, and then deprotonation to the products **29a-c**. The hydrolytic and oxidative ring transformation of compounds **29a-c** with selenium dioxide in water/acetic acid gave the 3-heteroaryl quinolone analogues **8a-c**, respectively, presumably *via* intermediates **W**-**Z** (Chart 5) [16] in a serial order as follows; the hydrolysis of compounds **29a-c** to an intermediate **W**, oxidation to an intermediate **X**, hydrolytic ring contraction to an intermediate **Z** *via* an intermediate **Y**, and then oxidation to the 3-heteroaryl quinolone analogues **8a-c**.

Scheme 9



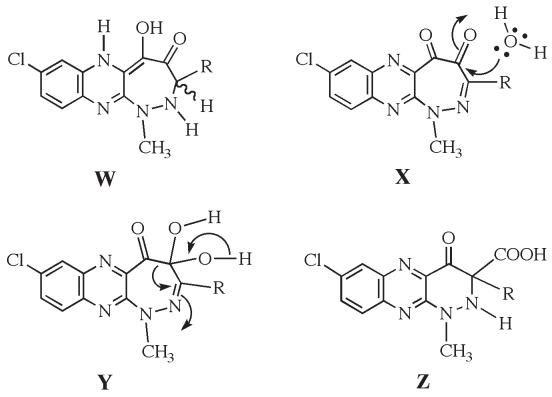
Reagents : (1) Heteroarylcarbaldehydes in Dioxane; (2) 2-Chloroacrylonitrile in Dioxane; (3) SeO_2 in H_2O/Acetic acid

Chart 4

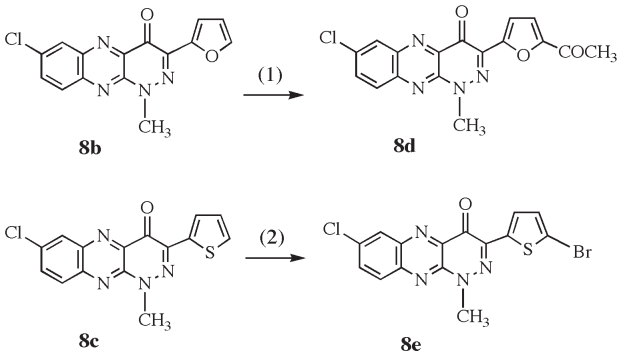


Compounds **8b** and **8c** were transformed into the 5'-acetyl and 5'-bromo derivatives **8d** and **8e**, respectively (Scheme 10).

Chart 5



Scheme 10



Reagents: (1) Acetic anhydride, $ZnCl_2$;
(2) *N*-Bromosuccinimide in Acetic acid

Nagao *et al*. have reported the intramolecular nonbonding 1,5-type S---O interaction for 1,3,4-thiadiazole derivatives **30** [17], wherein the acetyl group is included in the plane of the whole molecule (Chart 6). This intramolecular nonbonding 1,5-type S---O interaction was indicated for compound **8c** from the nmr spectral data. Namely, the 3'-H proton signals of the thiophene ring in compounds **29c** and **31** were observed in higher magnetic field than the 4'-H and 5'-H proton signals. However, the 3'-H proton signal of the thiophene ring in compound **8c** was observed in lower magnetic field than the 4'-H and 5'-H proton signals. The anisotropy for the 3'-proton of compound **8c** would be due to the inclusion of the 3'-proton and N_2=C_3 in the same plane.

Screening Data

Quinolone analogues **3-6** (Chart 7) had antimicrobial activities. Table 2 shows the *in vitro* antifungal activities of compounds **3**, **4**, and **6** to *Candida albicans, Candida krusei, Aspergillus flavas, Aspergillus fumigatus, Trichophyton mentagrophytes, and Trichophyton rubrum.* Table 3 exhibits the *in vitro* antibacterial and algicidal activities of compounds **3**, **5**, and **6** to *Aureobacididium pullulans, Bacillus subtilis, Cladosporium cladosporioides, Chaetonium globosum, Micrococcus luteus, Staphylococcus aureus* (bacteria) and to *Ankistrodesmus falcatus and Selenastrum capricorunutum* (algae), respectively.

Chart 6

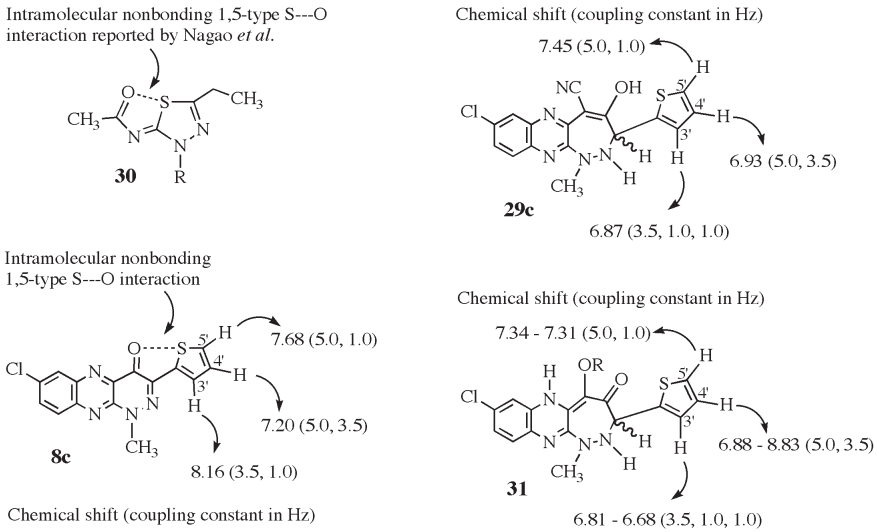


Chart 7

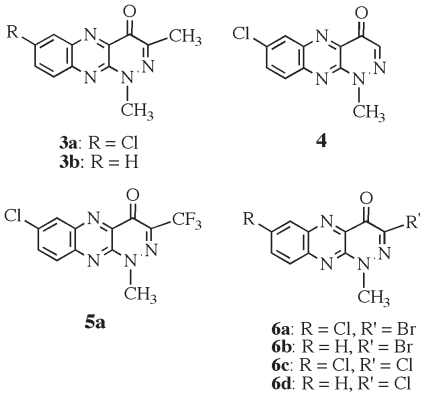


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Table 2
Screeninng Data of Compounds **3, 4,** and **6** to Several Fungi

	Minimum inhibitory concentration (mg/ml)					
Compound	*Candida albicans*	*Candida krusei*	*Aspergillus flavus*	*Aspergillus fumigatus*	*Trichophyton mentagrophytes*	*Trichophyton rubrum*
3a	4	4	8	8	2	2
3b	2	4	8	8	2	2
6a	4	2	-	-	1	1
6b	4	4	-	-	2	1
6c	4	2	-	-	1	0.5
6d	4	4	-	-	1	1
4	4	2	4	4	1	0.5
Itraconazole	0.031	0.5	0.25	0.5	0.125	0.031
Voriconazle	0.031	0.5	0.5	0.25	0.063	0.016

Table 3
Screening Data of Compoounds **3**, **5,** and **6** to Some Bacteria and Algae

	Minimum inhibitory concentration (mg/ml)							
Compound	*A. p.* [1]	*B. s.* [2]	*C. c.* [3]	*C. g.* [4]	*M. l.*[5]	*S. a.* [6]	*A. f.* [7]	*S. c.* [8]
3a	-	2	2	-	-	2	2	2
3b	-	3.9	-	2	-	-	-	-
5a	-	2	-	2	2	2	2	-
6a	2	2	2	2	2	2	2	2

(**Bacteria**): [1] *Aureobacididium pullulans*, [2] *Bacillus subtilis,* [3] *Cladosporium cladosporioides*, [4] *Chaetonium globosum*, [5] *Micrococcus luteus*, [6] *Staphylococcus aureus,*
(**Algae**): [7] *Ankistrodesmus falcatus*, [8] *Selenastrum capricorunutum*

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