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QUINOLONE COMPOUNDS WITH CARBOXYLIC EQUIVALENTS AND SEMIEMPIRICAL CALCULATIONS ON THEIR TAUTOMERS

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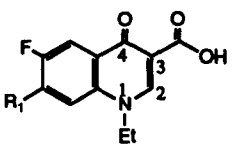
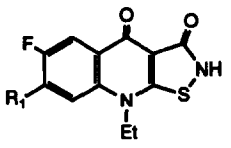
Abstract: Quinolone antibiotic compounds having no carboxylic group but its equivalents at the 3-position have been synthesized. Energies of tautomers with the carboxylic mimics were calculated in gas phase and aqueous solution with AM1-SCRF method. Antibacterial activity of the compounds was rationalized with tautomeric protons and atomic charges of calculated tautomers.

Quinolone antimicrobial agents have received attention because of their high efficacy. They are known to inhibit DNA gyrase (bacterial topoisomerase II) which introduces negative supertwist into DNA and separates interlocked DNA molecules.[1] Their mode of action on the molecular level has been proposed; among many essential structural elements, 3-carboxylic and 4-keto groups are thought to interact with DNA base pairs through hydrogen bonding.[2] Recently the carboxylic group has been modified to provide structural equivalent, and quinolones **2** with such equivalents show excellent activity against various bacteria.[3] Here we report the synthesis of several quinolones having 3-carboxylate-equivalents and the calculation of their conformation in gas phase and aqueous solution with a semiempirical molecular orbital method (AMPAC)[4] and a self-consistent reaction field (SCRF) method[5] and evaluate the structure-activity relationships.



1 Norfloxacin
R_1 = piperazyl



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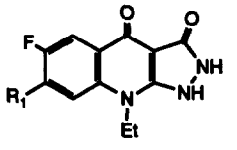

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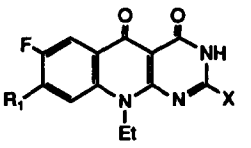
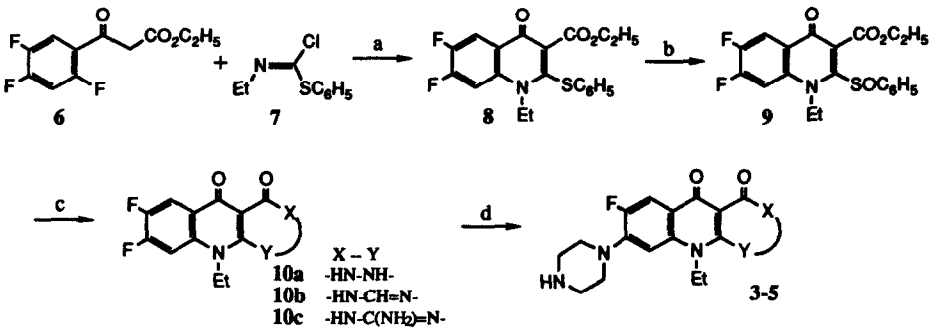


4 X = H
5 X = NH_2

Synthesis and Activity: Quinolone compounds **3-5** were synthesized from ethyl 1-ethyl-2-phenyl sulfinyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **9** as shown in Scheme I.[3] Displacement of the sulfinyl group of the sulfoxide **9** with hydrazine in dimethylformamide yielded 6,7-difluoro-9-ethyl-2,9-dihydro-1H-pyrazolo[3,4-b]quinoline-3,4-dione **10a** (70 %). Similar treatment of **9** with formamidine and guanidine yielded 7,8-difluoro-10-ethyl-3H,10H-pyrimido[4,5-b]quinoline-4,5-dione **10b** and 2-amino-7,8-difluoro-10-ethyl-3H,10H-pyrimido[4,5-b]quinoline-4,5-dione **10c**, respectively.

Scheme I



a) NaH, toluene b) mCPBA, CH_2Cl_2 c) HX--YH, DMF d) piperazine

Displacement of a fluorine on **10a,b,c** with piperazine at 100°C yielded the final quinolone compounds **3**, **4**, and **5**.[6] While compound **2** was known to be 4 times more active than norfloxacin **1**,[3b] products **4** and **5** show antibacterial activity of 1/16 and 1/60 time of that of norfloxacin **1**, respectively, and **3** shows no activity.

AM1-SCRF Calculation: The AM1-SCRF method has been successful in prediction of tautomeric equilibria for pyridone/hydroxypyridine[5c] and five-membered heterocycles.[5d] In this work, the piperazyl groups of **2-5** were modeled as NH_2 groups for simplicity, which would not affect the calculation of the tautomers of pyrazolo (**3**) and pyrimido (**4**, **5**) moieties. The heats of formation ΔH_f of each tautomers of interest and their anionic forms (Figure 1) were calculated with $\varepsilon = 1$ (corresponding to the gas phase) and $\varepsilon = 78.4$ (water)[7] and listed in Table 1.

Compound **2** is expected to exist mainly as form **2b** in aqueous solution ($\delta\Delta H_f = 1.3$ kcal/mol at $\varepsilon = 78.4$). Because there is only one ionizable proton in **2a** and **2b**, their ionic forms are equivalent and resemble carboxylate anions.[3b] Compound **4** was calculated to be a 1:1 mixture of **4a** and **4b** in solution (ΔH_f = -43.45 and -43.78 kcal/mol at $\varepsilon = 78.4$). Tautomeric isomers of **4** also have only one ionizable proton as in **2**, but anionic form of **4** can distribute the anionic charge further to the 4-keto-oxygen of the neighboring ring via resonance (see **4c**), even though the extent is expected to be not much according to comparison of the keto-bond lengthes of **2b**(-) and **4b**(-); 1.2444 and 1.2455 Å, respectively.

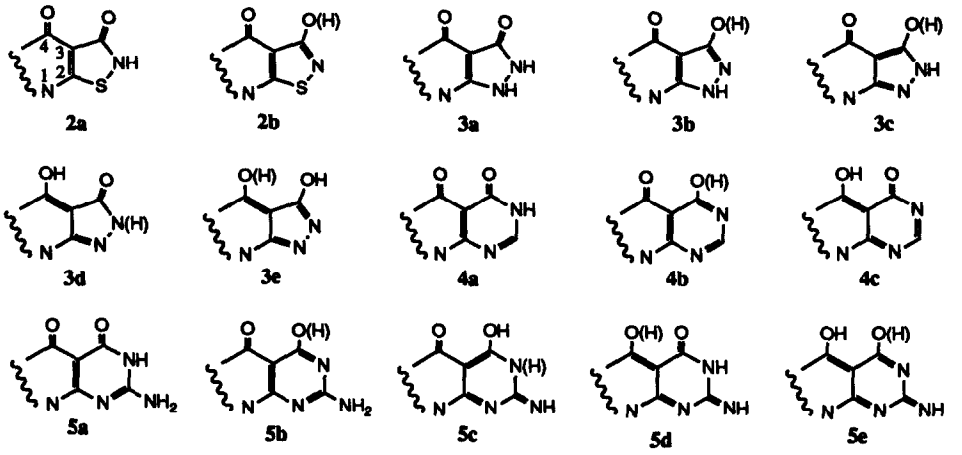
Among five possible tautomers of **3**, it is expected that in aqueous solution **3d** is a major component (ΔH_f = -23.11 kcal/mol) and **3c** and **3b** are minor tautomers (ΔH_f = -21.40 and -20.20 kcal/mol). For the anionic forms, however, it was calculated that both **3c**(-) and **3e**(-) are major anionic tautomers in aqueous solution (ΔH_f = -105.96 and -106.09 kcal/mol, respectively) and their keto-bond lengthes of **3c**(-) and **3e**(-) are 1.2511 and 1.2542 Å, respectively. In both anions, the keto-oxygens at the 4-position were affected to have more charge by resonance. One major difference among low-energy anionic tautomers of **2**, **4**, and **3**, is that the

Table 1. Calculated AM1 Heats of Formation for the Tautomeric Forms of Model Quinolones and Their Anionic Forms in Gas Phase and Aqueous Solution.

Quinolone	ΔH_f, kcal/mol		ΔH_f (anion[a])		Quinolone	ΔH_f, kcal/mol		ΔH_f (anion[a])	
	$\varepsilon = 1$	$\varepsilon = 78.4$	$\varepsilon = 1$	$\varepsilon = 78.4$		$\varepsilon = 1$	$\varepsilon = 78.4$	$\varepsilon = 1$	$\varepsilon = 78.4$
2a	-47.23	-52.12			**4a**	-40.65	-43.45		
2b	-49.31	-53.43	-77.66	-128.71	**4b**	-41.13	-43.38	-79.16	-120.04
3a	-3.80	-10.44			**4c**	-32.41	-36.77		
3b	-16.82	-20.20	-40.58	-90.60	**5a**	-36.27	-39.16		
3c	-20.52	-21.40	-66.06	-105.96	**5b**	-37.74	-39.42	-72.46	-108.81
3d	-21.31	-23.11	-48.82	-92.39	**5c**	-27.00	-27.76	-65.31	-104.45
3e	-13.85	-15.32	-65.81	-106.09	**5d**	-30.24	-33.01	-77.15	-114.15
					5e	-11.36	-13.94	-48.50	-93.55

[a] The protons to be removed are in parentheses in Figure 1.

Figure 1



first two anionic tautomers, **2b**(-) and **4b**(-), do not have an amide proton, but **3c**(-) and **3e**(-) do have amide protons. Therefore, the carboxylate mimics in **3c**(-) and **3e**(-) are similar to unionized carboxylic groups and cannot behave as anionic carboxylates (see Figure 1). Compound **5** could have also five different tautomeric conformers. In aqueous solution, the anionic forms of **5** will exist as a mixture of major **5d**(-) and minor **5b**(-) (ΔE = -5.3 kcal/mol), and the former has an amide proton and the latter has no amide proton. It is known that the pK_a of the 3-carboxylic groups of Norfloxacin **1** and its derivatives are about 6.1 and their biological efficacy is independent to the pK_a values.[3b] However, since most of quinolones including **1-4** have amino groups at the 7-position such as piperazyl groups, they are assumed to exist as zwitterions.[8]

While the calculated atomic charges of the 4-keto oxygens of the most stable anionic tautomers increase in

the order of **2b**(-) ≈ **4b**(-) < **5d**(-) < **3e**(-) (-0.3617, -0.3614, -0.3775, and -0.4400, respectively), the sums of the atomic charges of the equivalent ring-amide oxygens and nitrogens of the same anionic tautomers decrease; -1.0116, -0.7438, -0.5615, and -0.3644, respectively (protons are included in **3** and **5**, and that of **1** is -1.1549). This is the same increasing order of the ratio of the amide proton population in each stable tautomeric anion, and this is the reverse order of relative antibacterial activities of **2-5**.

In conclusion, the results of AM1-SCRF calculation and the relative biological activity suggest that any quinolones having carboxylic equivalents at the 3-position which can distribute anionic charge to the 4-keto-oxygen of quinolone agents and/or have unionizable protons at the 3-position even in anionic forms as in **3e**(-) and **5d**(-), are less potent. A previous study showed that 2-hydroxy substituted form of quinolone agents is inactive,[9] which also can be explained with the tautomerism; the more stable tautomer is expected to be the 2-keto-4-hydroxy form.[10]

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6. ^{1}H-NMR (CF_3CO_2D); for **3**, δ 8.25 (d, H), 7.33 (d, 1H), 4.67 (q, 2H), 3.98 (m, 4H), 3.79 (m, 4H), 1.65 (t, 3H); for **4**, δ 8.75 (s, 1H), 8.31 (d, 1H), 7.49 (d, 1H), 5.20 (q, 2H), 4.04 (m, 4H), 3.81 (m, 4H), 1.64 (t, 3H); for **5**, δ 8.05 (d, 1H), 7.15 (d, 1H), 5.15 (q, 2H), 4.03 (m, 4H), 3.82 (m, 4H), 1.64 (t, 3H)
7. The cavity radii (A0) were determined from a longest atomic distance of a molecule and van der Waals radii of two terminal atoms.[5c]
8. The pK_a of **10a**, **10b**, and **10c** are 10.20, 8.13, and 9.42, respectively, and the compound **3-5** may also exist as zwitterions since the pK_a of the conjugate acid of piperazine is kwown to be 9.8.[11]
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