Synthesis and Biological Evaluation of Some New Fused Quinazoline Derivatives

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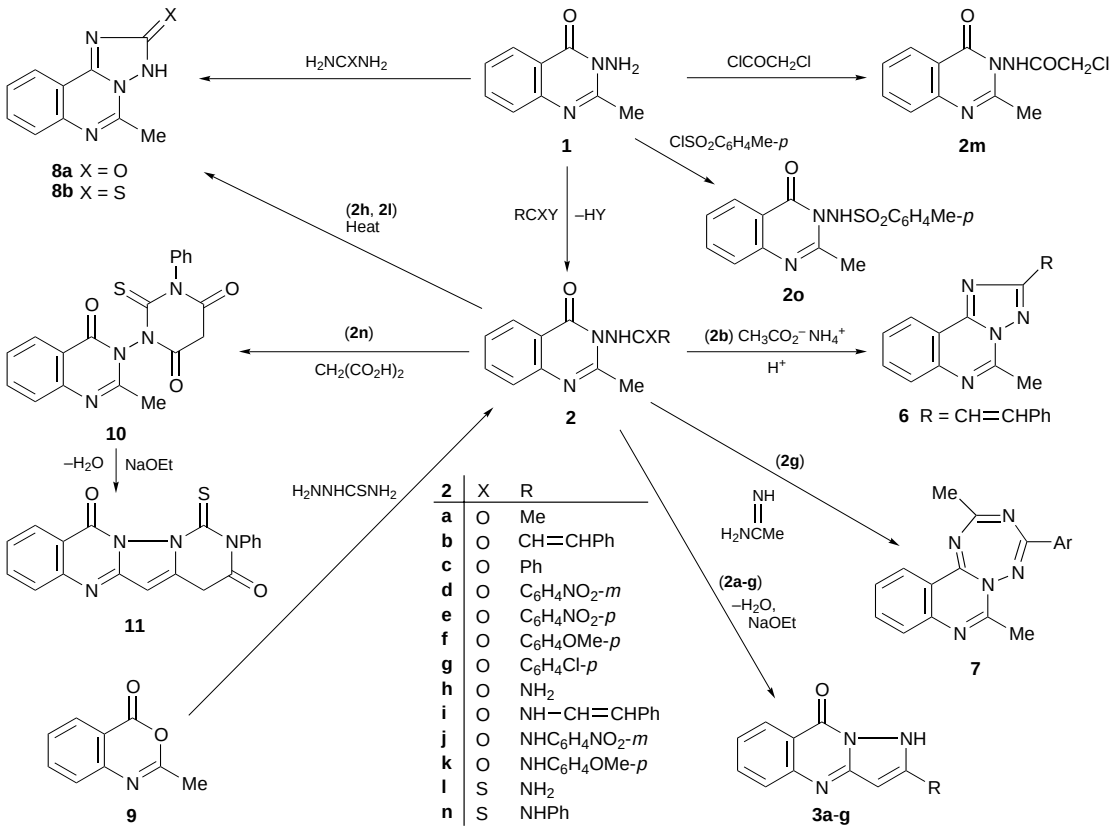
We report that biologically active fused quinazolines have been synthesized *via* treatment of 3-(*N*-acyl/aroylamino)quinazolin-4(3*H*)-ones (**2**) with various nucleophilic reagents; some of the products showed moderate antibacterial activity.

The present work describes the synthesis of some new fused quinazolines starting from 3-(*N*-acyl/aroylamino)-2-methylquinazolin-4(3*H*)-ones[11] (**2**) and their antimicrobial activity in order to establish a relation between structure and reactivity.

2-Substituted pyrazolo[5,1-*b*]quinazolin-9(1*H*)-ones (**3a–g**) were obtained by refluxing **2** with sodium ethoxide (Scheme IA). Acylation of **3e** followed by treatment with ammonium acetate–acetic acid[13] afforded the heterocyclic system **5** (Scheme II). Also, 2-cinnamyl-5-methyl-*s*-triazolo[2,3-*c*]quinazoline (**6**) and 4-(4-chlorophenyl)-2,7-dimethyl[1,2,4,6]tetrazepino[2,3-*c*]quinazoline (**7**) were isolated from refluxing **2b** with ammonium acetate–acetic acid and **2g** with acetamidine hydrochloride in sodium ethoxide[14] respectively. Investigations of the structure–activity relationships of **2h** and **2l** indicated that their activities are increased by fusion above their melting points to give 2-hydroxy/sulfanyl-5-methyl-*s*-triazolo[1,5-*c*]quinazolines (**8a**,**b**). Interestingly, it was found that **2n** on reaction with malonic acid in acetyl chloride[15] produced 1-(2-methyl-4-oxoquinazolin-3-yl)-3 phenyl-2,3-di-hydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (**10**) which on refluxing with sodium ethoxide gave the pyrimido[3′,4′:2,3]pyrazolo[5,1-*b*]quinazolinedione **11**. The IR spectrum of **11** showed characteristic absorption bands at ν_{max} 3194 (OH), 1692 (C=O), 2923 (CH_2, CH_3), 1316 (NCS) and 1109 cm^{-1} (C—S). The mass spectrum of **11** showed loss of Ph and H_2 to give a base peak at *m*/*z* 281.

Isomeric structures **12** and **13** were obtained respectively from treatment of **2m** with ammonium acetate–acetic acid and the interaction between **1** and chloroacetamide in *N*,*N*-dimethylformamide (DMF) (Scheme IB). The structures of **12** and **13** were deduced from their IR spectra which revealed bands at ν_{max} 3404 (OH), 3277, 3130 (NH), 2977, 2871 (CH_3, CH_2), 1657 (C=O) and 1608 cm^{-1} (cyclic C=C). The UV spectrum of **12** showed bands at λ_{max} 320, 306, 266 and 255 nm. Bands of this type are found with all aromatic azo compounds.[16]

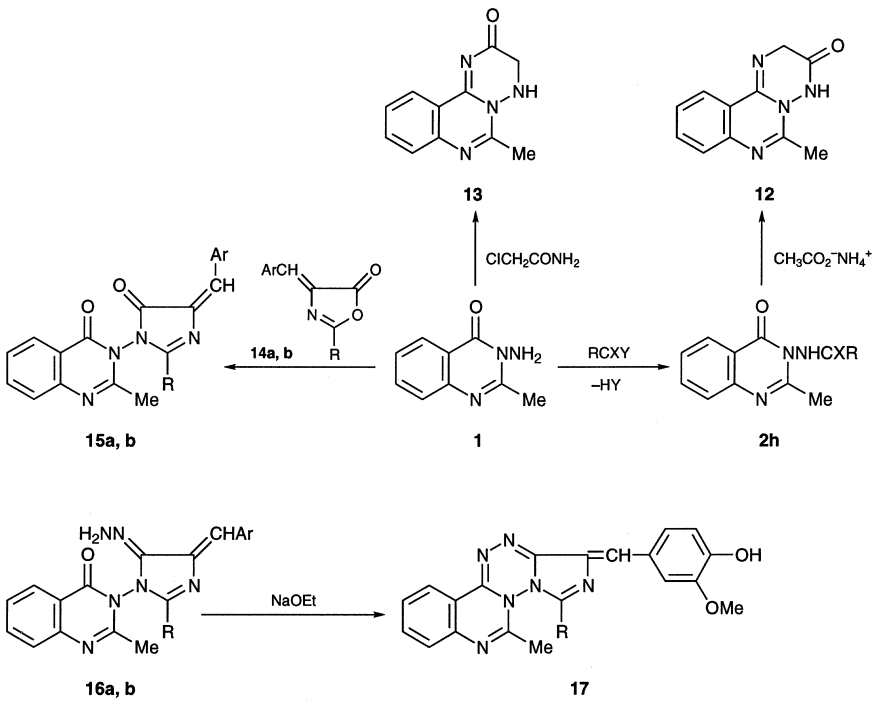
A convenient method for the synthesis of the fully fused quinazolines **17** was deduced from treatment of 2-methyl/phenyl-4-(arylmethylidene)oxazol-5(4*H*)-ones (**14a**,**b**) with **1** followed by cyclocondensation *via* hydrazinolysis in basic media. The IR spectrum of **17** showed disappearance of the NH_2, NH and C=O absorption bands, indicating the formation of a cyclic structure.



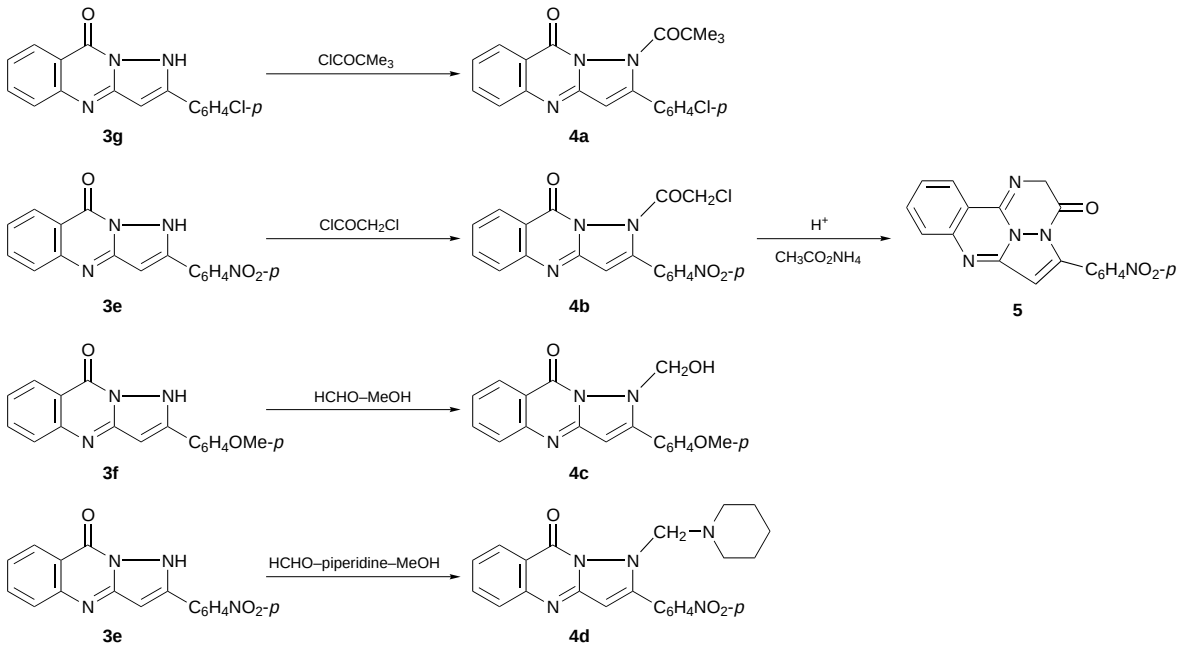
2	X	R
a	O	Me
b	O	CH=CHPh
c	O	Ph
d	O	$C_6H_4NO_2$-*m*
e	O	$C_6H_4NO_2$-*p*
f	O	C_6H_4OMe-*p*
g	O	C_6H_4Cl-*p*
h	O	NH_2
i	O	NH–CH=CHPh
j	O	$NHC_6H_4NO_2$-*m*
k	O	NHC_6H_4OMe-*p*
l	S	NH_2
n	S	NHPh

Scheme IA

*To receive any correspondence.



Scheme IB



Scheme IA

Measurements of the biocidal activity of some of the prepared compounds employing Cup-diffusion techniques[17] showed that **16a** is the most bactericidal and displays an effect[18] equal to that of gentamycin towards *E. coli.*

Techniques used: UV–VIS, IR, ^{1}H NMR and mass spectroscopy; X-ray and elemental analysis

References: 17

Table 1: Physical data for new compounds

Schemes: 3

Charts: 4 (Fragmentation patterns of compounds **2g**, **8a**, **11** and **13**)

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