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Synthesis of Triazolo and Pyrazolo Derivatives of Quinoline Nucleus

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Abstract:

New heterocyclic derivatives of quinoline are reported. Reaction of quinoline-2-thiol **4** with hydrazine hydrate gave 2-hydrazionoquinoline **5**. Treatment of **5** with CS_2 in pyridine afforded 1,2,4-triazolo-[4,3-a]-quinolin-1-2H-thione **6**, whereas the reaction of **5** with carboxylic acids namely formic acid or acetic acid, yielded the 1,2,4-triazol-[4,3-a]-quinolin **7** or 5-methyl-1,2,4-triazolo [4,3-a]-quinoline **8** through ring closure.

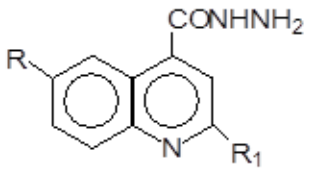
Diazotization of **5** under acidic conditions produced the fused tetrazole compound **9**, tetrzolo-[1,5-a]-quinoline. Moreover, treatment of **5** with active methlyene compounds gave two pyrazole derivatives **10** and **11**. Azomethines **12a-e** were prepared through condensation of **5** with aromatic aldehydes or ketones.

Keyword: triazoloquinoline, tetrazoloquinoline, pyrazoloquinolines, azomethines.

Introduction:

Quinoline derivatives are important organic bases because of their biological activity and their role as intermediary in the synthesis of a number of drugs and industrially important compounds.

Quinoline nucleus is part of many drugs and prodrugs, for example cinchonine and quinine are the first discovered drugs for treatment of malaria [1-4], where quinoline ring system is an integral part of their structure. Cinchoninic acid hydrazide **1** is a useful chemical in treatment of tuberculosis [5], whereas quinoline derivatives **2** are effective as antimalarial agents [6]. Few heterocyclics fused to quinoline ring are prepared and showed biological activity. One such compound is 1H-pyrrolo-[2,3-c]-quinoline **3** [7,8].



$R_1 = H, CH_3$

$R = OCH_3, OC_3H_7, OC_4H_9$

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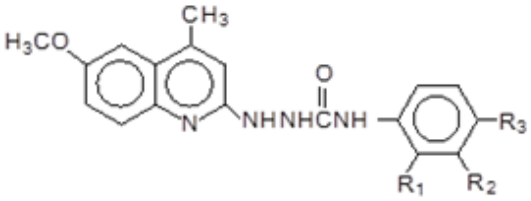

$R_3 = H \quad R_2 = H \quad R_1 = OCH_3$

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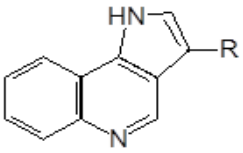

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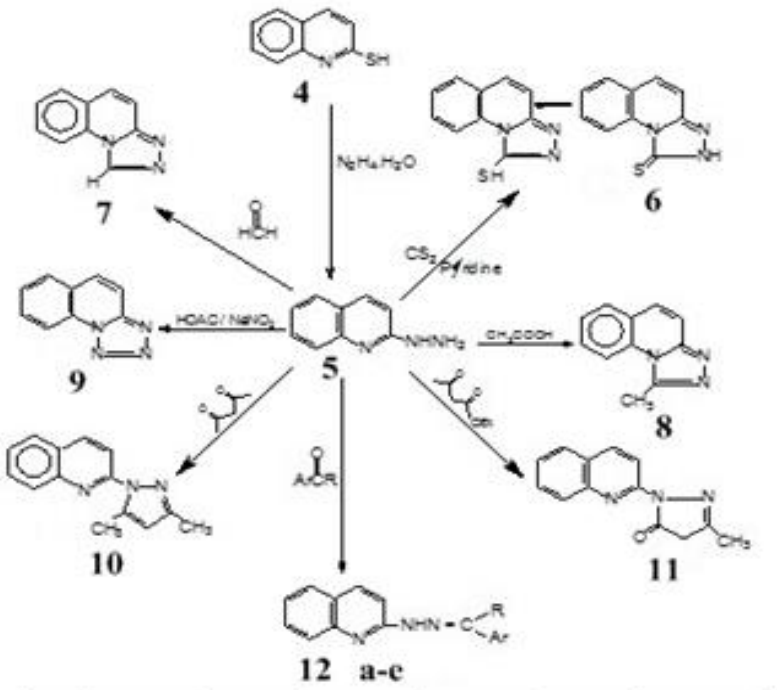
We now report on the synthesis of heterocyclic derivatives of quinoline with the purpose of investigating in the future their possible biological activities.

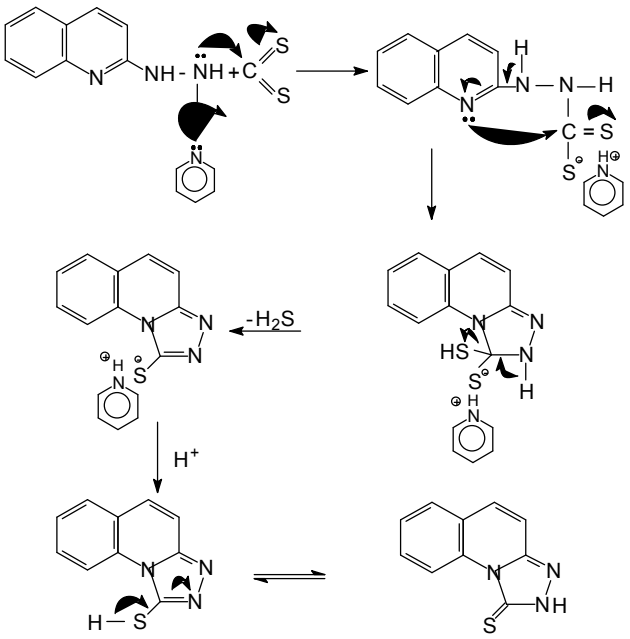
Results & Discussion:

Condensed triazolo and tetrazoloquinolines have been synthesized from 2-hydrazinoquinoline **5** which is obtained through reaction of quinoline-2-thiol **4** with hydrazine hydrate (scheme 1).



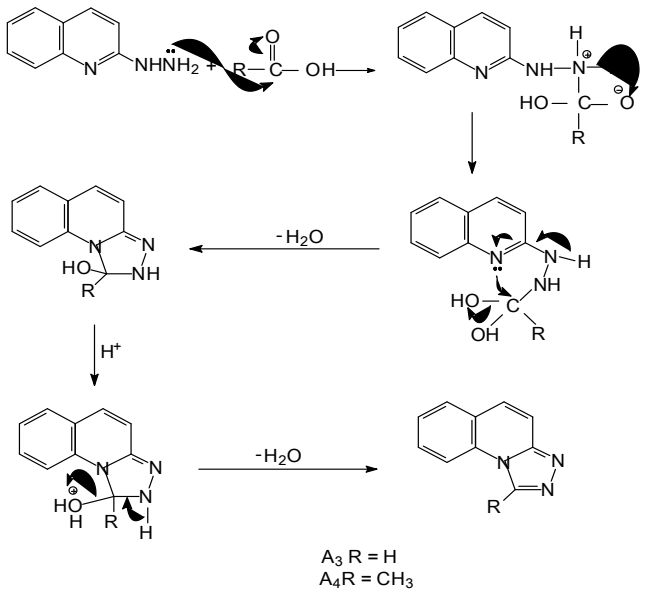
Scheme 1

Reaction of **5** with CS2 in pyridine afforded 1,2,4-triazolo-[4,3-a]- quinoline-1-2H-thione **2** in a good yield. The IR spectrum showed the N-H stretching absorption near 3083 cm^{-1} and the C=S stretching at 1267 cm^{-1} with a weak absorption near 2565 cm^{-1} due to S-H stretch because of thiol-thion tautomerism in **6** [9]. The mechanism of the intramolecular ring closure with CS_2 is shown in scheme 2.



Scheme 2

On the other hand, treatment of **5** with carboxylic acids, e.g. formic acid and acetic acid gave 1,2,4-triazolo-[4,3-a]-quinoline **7** or 5-methyl-1,2,4-triazolo-[4,3-a]-quinoline **8**. This ring closure is thought to proceed through nucleophilic attack of the nitrogen electron pair on the carbonyl of the carboxylic and followed by ring closing with elimination of two H_2O molecules (scheme 3).



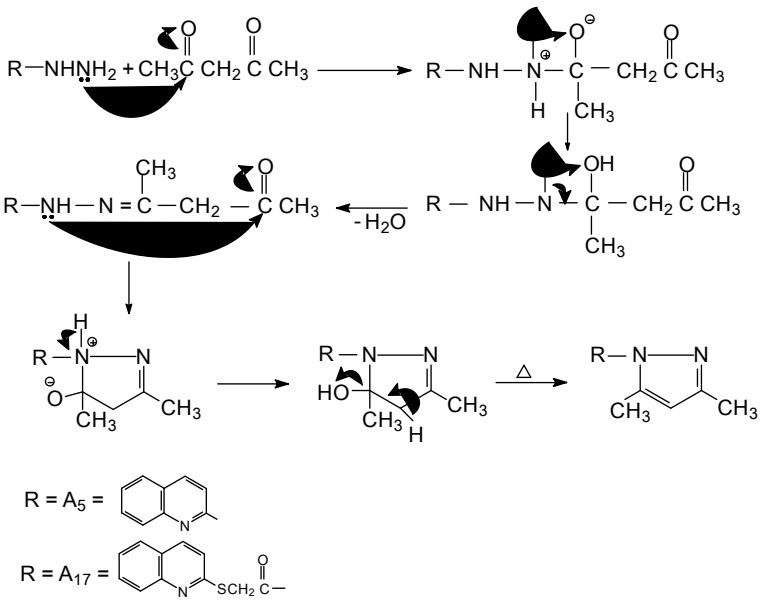
A_3 R = H
A_4R = CH_3

Scheme 3

The IR spectrum of **8** showed a band at 1375 cm^{-1} for the C-H bending in CH_3, in addition to the band at 1630 cm^{-1} for the C=N stretch. The ^{1}HNMR spectrum of **8** showed two doublets at 8.2 ppm and 7.85 ppm assigned to the pyridine ring protons and a singlet at 3.2 ppm for CH_3 protons and a multiplet at 7.6-7.7 ppm due to the benzene ring protons. ^{13}CNMR also agreed with the structure of **8**.

Future, diazotization of **5** under acidic conditions produced the fused tetrazole **9** namely, tetrazolo- [1,5-a]-quinoline [7.8]. The structure of **9** was confirmed by the appearance of the stretching band at 1610 cm^{-1} for C=N combined with the disappearance of the NH_2 stretching bands in addition to the band at 1085 cm^{-1} due to tetrazole ring[8].

Moreover, treatment of **5** with active methylene compounds yielded two pyrazolo derivatives **10** and **11**, thus the reaction of **5** with acetylacetone produced 2-(3,5-dimethyl-1H-pyrazol-1-yl) quinoline **10** in good yield, whereas the reaction of **5** with ethyl acetoacetate gave 5-methyl-1-2-quinolin-2yl-2,4-dihydro-3H-pyrazol-3-one **11** in 55-65% yield. The structure of **10** and **11** was confirmed by their IR and UV spectra through the appearance of the bands at 1371 cm^{-1} for CH_3 bending vibration in **10** and at 1720 cm^{-1} for C=O stretch in **11**, in addition to other characteristic absorptions (see experimental). The mechanism for the formation of pyrazole ring comprises the nucleophilic attack of the NH_2 electrons of **5** at the carbonyl carbon with elimination of a molecule of water followed by an internal nucleophilic attack on the other carbonyl carbon with ring closing (scheme 4).



Scheme 4

It is worth mentioning that **11** exists in keto-enol tautomeric forms indicated by the presence of weak absorption at 3250 cm^{-1} due to enolic O-H.

Condensation of 2-hydrazinoquinoline **5** with aryl aldehydes or ketones in absolute ethanol gave the Schiff's bases **12a-e**. The formation of Schiff's bases was indicated by the presence in their IR spectra the azomethine (CH=N) stretching band at 1600-1640 cm^{-1} combined with the disappearance of NH_2 stretching band**.**

Experimental:

General:

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra (KBr discs) were recorded with a Pye-Unicam SP3-100 or Shimadzu FTIR-8400. UV spectra were recorded on a Shimadzu 160A UV/VIS spectrophotometer using absolute ethanol as solvent.

^{1}HNMR and ^{13}CNMR spectra were obtained with AVS-400 Hanover University-Germany in $CDCl_3$ with TMS as an internal standard. Starting chemical compounds were obtained from Fluka or BDH.

Preparation of 2-hydrazinoquinoline 5:

A mixture of quinoline-2-thiol (0.01 mole) and hydrazine hydrate 90% (20-30 ml) was gently refluxed for 3 hours. After cooling, water (20 ml) was added and the solid was collected by filtration, washed with distilled water and recrystallized from ethanol-water. Compound **5**, m.p. 140-142 ^{o}C; 65% yield; R_f = 0.81 (AcOEt); IR (v, cm^{-1}): 3295, 3190 (N-H), 1577, 1488 (C=C), 1639 (C=N); UV (λ_{max}): 242, 337 nm.

Preparation of 1,2,4-triazolo-[4,3-a]-quinolin-1-(2H)-thione 6:

To a solution of **5** (0.003 mole) in dry pyridine (10 ml), carbon disulfide (5 ml) was added. The mixture was heated under reflux for 5 hours, cooled and (10 ml) of benzene with few drops of conc. HCl were added. The solvent was evaporated, water (10 ml) was added and the solid was collected by filtration, washed with distilled water and recrystallized from ethanol. Compound **6**, m.p. 268-272 ^{o}C; yield 80%; IR (v, cm^{-1}): 3083 (NH), 1640 (C=N), 1604 (C=C), 1267 (C=S); UV (λ_{max}, ϵ_{max}): 262 nm, 12600; 305 nm, 15940; R_f = 0.67 (Acetone-$CHCl_3$, 1:2).

General procedure for preparation of 1,2,4-triazolo-[4,3-a]-quinoline 7 and 5-methyl-1,2,4-triazolo-[4,3-a]-quinoline 8:

The solution of compound **5** (0.003 mole) in formic acid (5 ml) or glacial acetic acid (10 ml) was heated under reflux for 5 hours. The solvent was evaporated under *vacuo* as much as possible and the mixture was poured onto ice-cold water. The solid was filtered, washed with water and recrystallized from ethyl acetate. Compound **7**, m.p. 164-167 ^{o}C; yield 65%; IR (v, cm^{-1}): 3090 (C-H_{Ar}), 1620 (C=N), 1590, 1450 (C=C), 1250 (C-N); UV (λ_{max}, ϵ_{max}): 302 nm, 18090. Compound **8**, m.p. 158-160 ^{o}C; yield 70%; IR (v, cm^{-1}): 3080 (C-H_{Ar}), 1630 (C=N), 1590, 1450 (C=C), 1320 (C-N), 1375 (CH_3); UV (λ_{max}, ϵ_{max}): 239 nm, 16610, 291 nm, 14240; R_f = 0.40 ($CHCl_3$-AcOEt, 2:1). ^{1}HNMR δ: 3.2 (s, CH_3), 8.2 (d, 1H, H_1 pyridine ring), 7.85 (d, 1H, H_2 pyridine ring), 7.75-7.60 (m, 4H, benzene); ^{13}CNMR: 149.6, 132.0, 129.8, 129.5, 126.2, 124.6, 115.8, 114.9, 16.2 .

Preparation of tetrazolo-[1,5-a]-quinoline 9:

The solution of **5** (0.001 mole) in glacial acetic acid (3 ml) was cooled to 0 ^{o}C in an ice bath. A solution of sodium nitrite (0.001 mole) in water (3 ml) was added portion-wise with continuous stirring for 16 hours. Excess acid was evaporated in *vacuo* and the solid product was recrystallized from ethanol; m.p. 150-153 ^{o}C; yield 60%; IR (v, cm^{-1}): 3030 (C-H_{Ar}),1560, 1527. 1446 (C=C) 1610 (C=N), 1134, 1085, 1030 (tetrazole) [8]; UV (λ_{max}, ϵ_{max}): 236 (7730), 273 (3210), 302 (1640), 316 (1190): R_f = 0.70 ($CHCl_3$-AcOEt, 2:1).

General procedure for preparation of 2-(3,5-dimethyl-1H-pyrazol-1-yl) quinoline 10 and 5-methyl-2-quinoline-2-yl-2,4-dihydro-3H-pyrazol-3-one 11:

To a solution of compound **5** (0.002 mole) in absolute ethanol (30 ml) was added acetylacetone (0.002 mole) or ethyl acetoacetate (0.002 mole). The reaction mixture was heated at reflux for 6 hours and after cooling the precipitate was filtered and recrystallized from MeOH-H_2O. Compound **10**, m.p. 60-61 ^{o}C; yield 63%; IR (v, cm^{-1}): 3030 (C-H_{Ar}), 2922-2856 (C-H), 1606 (C=N), 1557, 1504 (C=C), 1371 (δCH_3); UV (λ_{max}): 285, 328, 385 nm. Compound **11**, m.p. 132-134 ^{o}C; yield 55%; IR (v, cm^{-1}): 3030 (C-H_{Ar}), 2980 (C-H), 1720 (C=O), 1600 (C=N) 1530, 1480 (C=C), 1380 (δCH_3); UV (λ_{max}, ϵ_{max}): 327 nm (22710); R_f = 0.62 ($CHCl_3$-AcOEt, 2:1).

Preparation of compounds 12a-e:

A mixture of **5** (0.01 mole) and the corresponding aryl aldehyde or aryl ketone (0.01 mole) in ethanol (30 ml) was refluxed for 3 hours and cooled. The solid product was filtered and recrystallized from ethanol. **12a**: (R = H, Ar = p-BrC_6H_4); yield 90%; m.p. 180-182 ^{o}C; IR (v, cm^{-1}): 3220 (N-H), 3080 (C-H_{Ar}), 1640 (C=N), 1590, 1520 (C=C); UV (λ_{max}): 237, 346 nm. **12b**: (R = H, Ar = m-$NO_2C_6H_4$); yield 85%; m.p. 218-220 ^{o}C; IR (v, cm^{-1}): 3200 (N-H), 3030 (C-H_{Ar}), 1640 (C=N), 1570, 1460 (C=C); UV (λ_{max}): 287, 346 nm. **12c**: (R = H, Ar = p-OHC_6H_4); yield 80%; m.p. 252-254 ^{o}C; IR (v, cm^{-1}): 3400 (N-H), 1640 (C=N), 1600, 1530 (C=C); UV (λ_{max}):

318 nm. **12d**: (R = CH_3, Ar = p-$NH_2C_6H_4$); yield 88%; m.p. 138-140 ^oC; IR (v, cm^{-1}): 3480, 3380 (NH_2), 3220 (N-H), 3030 (C-H_{Ar}), 1635 (C=N), 1610, 1540 (C=C); UV (λ_{max}): 232, 317 nm. **12e**: (R=CH_3, Ar = m-$NO_2C_6H_4$); yield 90%; m.p. 172-174 ^oC; IR (v, cm^{-1}): 3250 (N-H) 3040 (C-H_{Ar}), 1640 (C=N), 1600, 1550 (C=C), 1520, 1340 (NO_2); UV (λ_{max}): 281, 340 nm.

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