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Synthesis and biochemical screening of some new quinolino[3,2-*c*]oxazines

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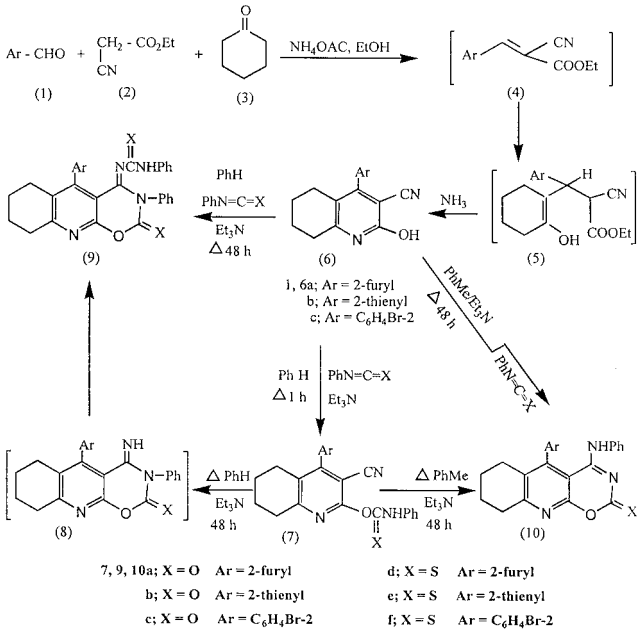
Quinolines and quinolines containing oxazine moiety such as ciprofloxacin [1, 2], and olfloxacin [3] were found to exhibit important biological and biochemical activities. On the other hand the presence of a heterocyclic ring such as furo [4] and thieno [5] at different positions of the quinoline moiety enhanced activity [6]. This prompted us to synthesize some new quinolino[3,2-*c*]oxazines containing furan and thiophene moieties as biochemically active compounds.

Scheme



2-Hydroxy-4-aryl-5,6,7,8-tetrahydroquinoline-3-carbonitriles **6a–c** were obtained via the reaction of aromatic aldehydes **1a–c**, ethyl cyanoacetate (**2**) and cyclohexanone (**3**) in the presence of ammonium acetate [7, 8]. Structures of **6a**, **c** are consistent with the microanalysis, IR, ^{1}H NMR and MS.

This paper describes the base catalyzed reaction of phenyl isocyanate or phenyl isothiocyanate with **6**, to form labile carbamates **7a–f**. Thus addition of triethyl amine, as a catalyst, allows the formation of compounds **7a–c** in 1 h instead of 24 h in dry benzene only.

Cyclization of **7a–f** was attempted by the action of triethyl amine in refluxing benzene, where the carbamoylimino derivatives **9a–f** were obtained instead of the expected iminoquinolinoxazine **8**. Triethyl amine catalyzed the intramolecular N–H addition to the carbonitrile triple bond, where the formed intermediate **8** reacted with phenyl isocyanate or phenyl isothiocyanate, resulted from partial decomposition of **7** [9], to form **9**. Compounds **9a–f** were also obtained in one step through equimolar reaction of **6** with phenyl isocyanate or phenyl isothiocyanate in the presence of triethyl amine. The reaction yield was greatly improved when using two mols of isocyanates or isothiocyanates.

Cyclization of **7a–f** using a higher boiling solvent as toluene allows the formation of 5-aryl-4-anilino-6,7,8,9-tetrahydroquinolino[3,2-*c*]oxazine-2-ones **10a–c** or 2-thiones **10d–f**. This indicates that the higher reaction temperature causes a Dimroth rearrangement of the intermediate **8** to take place [10]. Compounds **10a–f** are also obtained in one step via Dimroth rearrangement by refluxing compound **6**, phenyl isocyanate or phenyl isothiocyanate and triethyl amine in either toluene or dimethylformamide [11] for 48 h and 12 h, respectively.

Experimental

M.p.'s were uncorrected. IR spectra were measured on a PYE Unicam SP 1000 spectrophotometer. ^{1}H NMR spectra were measured on a

Table 1: Physical data of compounds prepared

Compd.	M.P. (°C)	Formula	Yield (%)	Compd.	M.P. (°C)	Formula	Yield (%)
7a	213–215	$C_{21}H_{17}N_3O_3$	71	**9d**	95– 97	$C_{28}H_{22}N_4O_2S_2$	72
7b	220–222	$C_{21}H_{17}N_3O_2S$	77	**9e**	103–105	$C_{28}H_{22}N_4OS_3$	69
7c	218–220	$C_{23}H_{18}N_3O_2Br$	80	**9f**	128–130	$C_{30}H_{23}N_4OS_2Br$	64
7d	214–216	$C_{21}H_{17}N_3O_2S$	65	**10a**	238–240	$C_{21}H_{17}N_3O_3$	61
7e	145–147	$C_{21}H_{17}N_3OS_2$	72	**10b**	232–234	$C_{21}H_{17}N_3O_2S$	73
7f	181–183	$C_{23}H_{18}N_3OSBr$	66	**10c**	236–238	$C_{23}H_{18}N_3O_2Br$	70
9a	246–248	$C_{28}H_{22}N_4O_4$	73	**10d**	130–132	$C_{21}H_{17}N_3O_2S$	72
9b	243–245	$C_{28}H_{22}N_4O_3S$	70	**10e**	118–120	$C_{21}H_{17}N_3OS_2$	68
9c	251–253	$C_{30}H_{23}N_4O_3Br$	72	**10f**	96– 98	$C_{23}H_{18}N_3OSBr$	67

Table 2: SGOT, SGPT, creatinine and urea

Compd.		GOT (μkat/l)	GPT (μkat/l)	Creatinine (mg%)	Urea (g/l)
Control	Mean ± SEM	40.5 ± 1.025	35.6 ± 1.15	0.702 ± 0.19	0.177 ± 0.017
6a	Mean ± SEM	43.5 ± 1.34	38.6 ± 1.57	0.629 ± 0.02	0.259 ± 0.02
	$p <$	0.05	0.10	0.0125	0.005
9a	Mean ± SEM	41.5 ± 0.72	36.8 ± 1.06	0.634 ± 0.015	0.289 ± 0.02
	$p <$	0.25	0.25	0.01	0.0005

EM NMR spectrometer 200 MHz PMR using DMSO-d_6 as a solvent and TMS as internal reference. MS were run on a HP MODEL: MS 5988 (70 eV). The results of elemental analysis for C, H and N were within ±0.3% of the theoretical values.

1. Preparation of the starting materials

The synthesis of 2-hydroxy-4-(2-thienyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**6b**) is described in the literature [16].

2. 2-Hydroxy-4-(2-furyl) or (2-bromophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (6a, c)

Equimolar amounts (0.01 mol) of each (**1a**, **c**), ethyl cyanoacetate (**2**) and cyclohexanone (**3**) in EtOH (50 ml) were heated in the presence of ammonium acetate (0.015 mol) for 15 min, then stirred for 3 h. The solid product was collected by filteration and recrystallization from dioxan to give **6a**, **c**, respectively.
6a: Yield 79%, m.p.: >280 °C, IR (KBr, cm^{-1}): 3500 (OH), 2200 (C≡N); MS: m/z 240 (4.22, M^+), 241 (0.64, M + 1), 93 (100).
6c: Yield 68%, m.p.: >280 °C, IR (KBr, cm^{-1}): 3500 (OH), 220° (C≡N). ^{1}H NMR **6c** (DMSO-d_6): δ (ppm) = 1.8 (s, 4 H, 2 CH_2 cyclo), 2.9 (s, 4 H, 2 CH_2 cyclo), 7,0–7.6 (m, 4 H, Ar–H), 9.2 [s, 1 H, N–H].

3.4-Aryl-2-(phenylaminocarbamoyloxy or phenylaminothiocarbamoyloxy)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (7a–f)

3.1. Method A

A solution of **6** (0.01 mol), (0,01 mol) of phenyl isocyanate or phenyl isothiocyanate in dry benzene was refluxed for 24 h to yield **7a–f**.
7a–c: IR (KBr, cm^{-1}): 3150–3400 (NH), 2200–2225 (C≡N), 1680–1700 (C=O).
7d–f: IR (KBr, cm^{-1}): 3200–3380 (NH), 2200–2220 (C≡N), 1280–1340 (C=S).
^{1}H NMR **7d** (DMSO-d_6): δ (ppm) = 1.7 (s, 4 H, 2 CH_2 cyclo), 2.6 (s, 4 H, 2 CH_2 cyclo), 6.7–8.7 (m, 8 H, Ar–H), 12.2 (s, 1 H, NH); ^{1}H NMR **7e** (DMSO-d_6): δ (ppm) = 1.6 (s, 4 H, 2 CH_2 cyclo), 2.6 (s, 4 H, 2 CH_2 cyclo), 7.1–8.8 (m, 8 H, Ar–H), 12.1 (s, 1 H, NH); MS **7b**: m/z 375 (2.96, M^+), 256 (100); MS **7d**: m/z 375 (0.7, M^+), 93 (100); MS **7e**: m/z 391 (0.3, M^+), 194 (100).

3.2. Method B

A solution of **6** (0.01 mol), (0.01 mol) of phenyl isocyanate or phenyl isothiocyanate in dry benzene was refluxed in the presence of 3 drops of TEA for 1 h to yield **7a–f**.

4.5-Ary-4-[N-(N-phenylcarbamoyl or N-phenylthiocarbamoyl)imino]-3-phenyl-6,7,8,9-tetrahydroquinolino[3,2-c]oxazine-2-ones 9a–c *or 2-thiones* 9d–f

4.1. Method A

A solution of **6** (0.01 mol), phenyl isocyanate or phenyl isothiocyanate (0.01 mol or 0.02 mol) and 4 drops of TEA was refluxed for 48 h to yield **9a–f**.
9a–c: IR (KBr, cm^{-1}): 3180–3420 (NH), 1660–1700 (2 C=O); **9d–f**: IR (KBr, cm^{-1}): 3250–3400 (NH), 1310–1350 (2 C=S); ^{1}H NMR **9a** (DMSO-d_6): δ (ppm) = 1.7 (s, 4 H, 2 CH_2 cyclo), 2.6 (s, 4 H, 2 CH_2 cyclo), 6.9–7.4 (m, 13 H, Ar–H), 8.7 (s, 1 H, NH); MS **9b**: m/z 494 (0.13, M^+), 93 (100).

4.2. Method B

A mixture of **7a–f** (0.01 mol), dry benzene (10 ml) and 4 drops of TEA was refluxed for 48 h to yield **9a–f**.

5. 5-Aryl-4-anilino-6,7,8,9-tetrahydroquinolino[3,2-c]oxazine-2-ones 10a–c *or 2-thiones* 10d–f

5.1. Method A

To a solution of **6** (0.01 mol) in toluene (10 ml) were added 0.01 mol or 0.02 mol of phenyl isocyanate or phenyl isothiocyanate and 3 drops of TEA. The resulting mixture was heated under reflux for 48 h to yield **10a–f**.
10a–c: IR (KBr, cm^{-1}): 3220–3410 (NH), 1670–1700 (C=O). **10d–f**: IR (KBr, cm^{-1}): 3200–3390 (NH), 1280–1320 (C=S). ^{1}H NMR (**10c**) in DMSO-d_6 (δ ppm): 1.8 (s, 4 H, 2 CH_2 cyclo), 2.8 (s, 4 H, 2 CH_2 cyclo), 6.9–7.5 (m, 9 H, Ar–H), 8.6 (s, 1 H, NH). MS (**10c**): m/z 448 (0.8, M^+), 93 (100). MS (**10d**): m/z 375 (0.5, M^+), 194 (100).

5.2. Method B

A mixture of **7a–f** (0.01 mol), (10 ml) of toluene and 3 drops of TEA was refluxed for 48 h to yield **10a–f**.

5.3. Method C

A mixture of **6** (0.01 mol) in DMF (10 ml) were added to (0.01 mol) of phenyl isocyanate or phenyl isothiocyanate and 3 drops of TEA, then heated under reflux for 12 h to yield **10a–f**.

6. Biochemical screening

Three groups of male albino rats weighing (100–120 g) were submitted for this study. Group (a) as control was given a mixture of Tween 80 and distilled water, while groups (b) and (c) were orally administrated daily for 28 d with a dose of 50 mg/kg body weight from compounds **6a** and **9a**, suspended in a mixture of Tween 80 and distilled water. After 28 d of treatment, the animals were sacrified and blood obtained was tested for liver function SGPT (serum-glutamate-pyruvat-transaminase) and SGOT (serum-glutamate-oxalactate-transaminase) [12]. Kidney function was also assessed by measurement of serum creatinine and urea [13, 14]. Results were expressed as the mean ± SEM and statistically evaluated by student's "t" test. A difference between two means was considered significant with $p \leq 0.05$ [15].
Compound **6a** showed a significant increase in the SGOT and SGPT levels of the treated animals, while compound **9a** showed no significant changes (Table 2). On the other hand both compounds (**6a** and **9a**) showed a significant increase in the urea levels accompanied with a significant decrease in creatinine levels.

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