Synthesis of Triazoles, Oxadiazoles and Condensed Heterocyclic Compounds Containing Cinchopheny and Studies on Biological Activity of Representative Compounds

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Compounds 2-arylamino-5-cinchophenyl-1,3,4-oxadiazoline (**7**) and 3-thio-4-amino-5-cinchophenyl-1,2,4-triazole (**3**) have been synthesized utilizing cinchophen as the starting material. The compound 3-cinchopheny-s-triazolo[3,4-*b*]-1,2,3,4-thiatriazole (**4**) was prepared from compound **3**. Condensation of **3** with aromatic acid in the presence of $POCl_3$ gave 10 new 6-aryl-3-cinchopheny-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**5**). Some of the representative compounds were screened for antibacterial activity. The structures of these new compounds have been confirmed by means of elemental analysis, IR, ^{1}H NMR and MS.

Keywords: Cinchophen; Synthesis; Triazoles; Oxadiazoles; Condensed heterocyclic compounds; Biological activity.

INTRODUCTION

The derivatives of 1,2,4-s-triazole and 1,3,4-thiadiazole possess broad-spectrum biological activities and many other uses.[1-5] There have been more and more reports on these fused heterocyclic compounds; the studies on them have been very active since M. Kanaoka[6] first condensed these two cyclic compounds into one molecule to yield s-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives. These papers indicate that the triazolothiadiazole 3,6-substituted by aryl, alkyl or heterocyclic radical possesses broad-spectrum biological activities such as antibacterial,[7] anti-inflammatory,[8] herbicidal,[9] plant growth regulative activity[10] and anti-HIV-1 activities.[11] Though a lot of reports on s-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives are available, their derivatives 3,6-substituted by alkyl, aryl, alkoxyl or 3-substituted by heterocyclic radical are rarely reported.

As is well known, 2-phenlquinolyl-4-carboxylic acid (cinchophin) displays antifebrile anodyne, antirheumatic and glucosuria metabolic activities, etc.,[12] but it has become obsolete in recent years due to its side-effects in clinical use. With a view to explore other uses of cinchophin, we decided to use cinchophin as parent material to synthesize some new derivatives. So, we decided to combine 2-phenyquinolyl to oxadiazole or condensed heterocycle in order to obtain new heterocyclic compounds exhibiting promising biological activity.

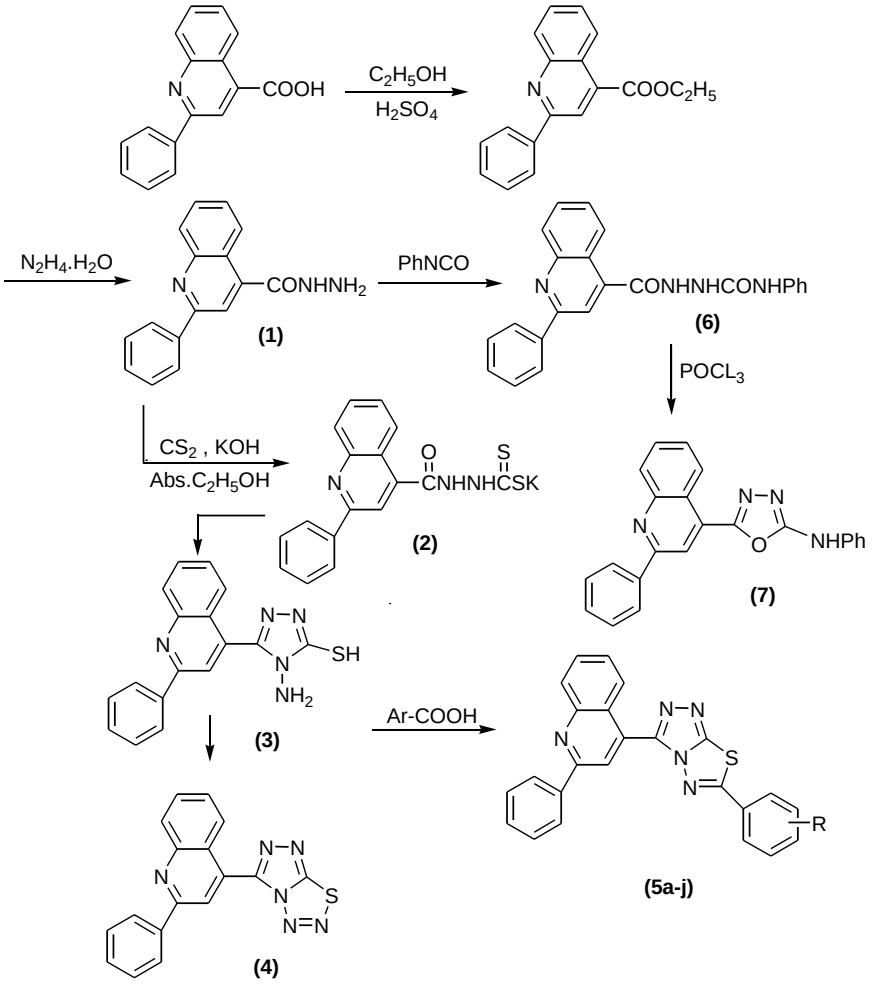
RESULTS AND DISCUSSION

The synthesis of compounds: the synthesis of all compounds was accomplished as shown in Scheme I.

After esterification and hydrazinolysis, cinchophen was converted to 2-phenylquinolyl-4-formylhydratide (**1**) which was refluxed with isocyanate in absolute ethanol to give compound **6** which was changed to compound **7** in $POCl_3$. Compound **1** reacted with CS_2 in KOH absolute ethanol solution to give 2-phenylquinolyl-4-potassium formylhydrazino dithioformate (**2**) which was refluxed in excess hydrazine hydrate to obtain 3-(2-phenylquinolyl-4-yl)-4-amino-5-thio-1,2,4-triazole (**3**). Compound **3** was refluxed with substituted benzoic acid in $POCl_3$ to yield desired compounds **5a-j**.

In order to explore biological properties of cinchophen we designed such methods that involved diazotization reaction of parent compound 3-(2-phenylquinolyl-4-yl)-4-amino-5-thio-1,2,4-triazole (**3**). As compound **3** has 5-thio and 4-amino simultaneously, the formed diazonium could cyclize with thiohydroxy to give triazolothiatriazole. We referred to the papers on compound **4** and found that A. K. El-Shafei, in 1982, utilized 3-thio-4-amino-5-phenyl-1,2,4-triazole as

Scheme I



5a R = *p*-Cl, **5b** R = *p*-F, **5c** R = *p*-I, **5d** R = *p*-CH_3, **5e** R = *p*-Br
5f R = *m*-F, **5g** R = *m*-Cl, **5h** R = *m*-CH_3, **5i** R = *m*-Br, **5j** R= *o*-Cl

starting material to realize diazotization reaction in $NaNO_2$/HCl at 0 °C. The diazonium spontaneously coupled to give 5-phenyl-1,2,4-triazolo[3,4-*b*]-1,2,3,4-thiatrizole. The IR data of compound **4** accorded with those of the compounds synthesized by A. K. El-Shafei.

Because of no proton on the condensed ring of compounds **5a-j**, their ^{1}H NMR spectra consisted only of the benzene ring proton absorption peaks. The single peaks at δ 2.41 and δ 2.42 appeared owing to the methyl on 6-aryl of compounds **5d** and **5h**. The detailed ^{1}H NMR data are listed in Table 2.

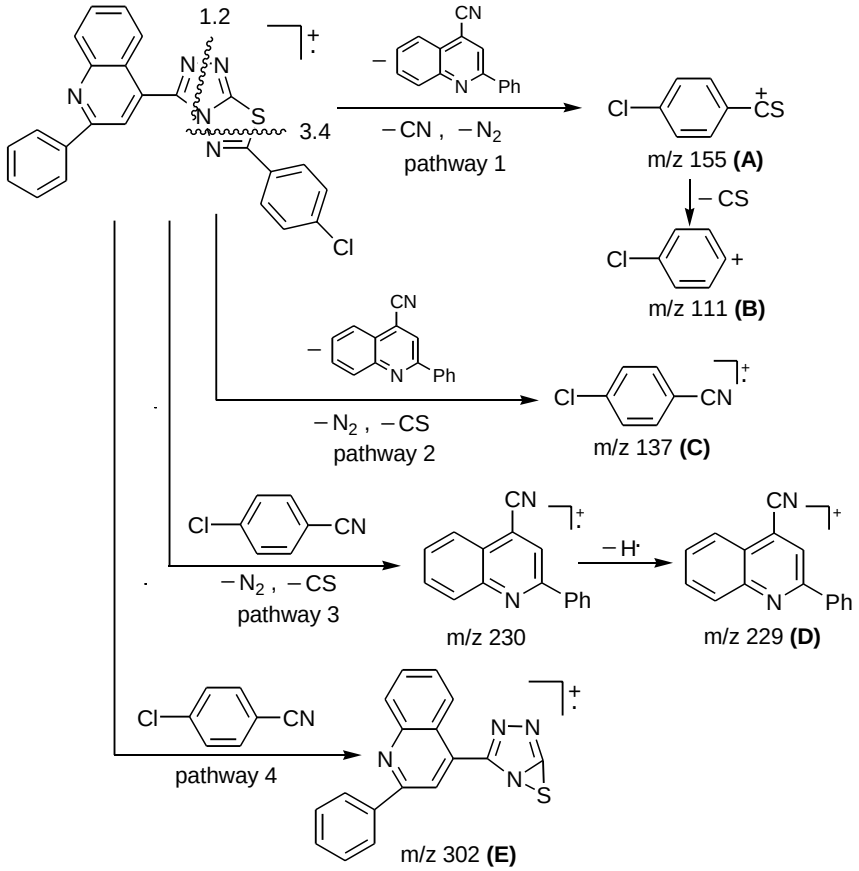
As Table 3 shows, five representative compounds of compound **5** had strong isotope peaks to the halogen on them. Their molecule ion peaks were strong resulting from aryl.

All compounds exhibited *m/z* 229, *m/z* 230 and *m/z* 302 piece peaks. We chose compound **5a** to investigate its scission mechanism, as shown in Scheme II.

EXPERIMENTAL SECTION

Melting points were determined on a National X_4 microscropic melting point apparatus and are uncorrected. The IR spectra (KBr) were obtained on a Nicolet FT-IR170SX spectrophotometer; ^{1}H NMR spectrum was recorded on a FT-80A instrument in DMSO-d_6 with TMS as internal stan-

Scheme II



dard. Mass spectrum was on a VG-7070 spectrometer and elemental analysis was on an Elementar Vario EL analyzer.

Ethyl cinchophenate (mp 51 °C) and cinchopen hydrazide (mp 223-225 °C)

These were prepared by the reported methods and their melting points were measured with those therein.

3-Cinchophenyl-4-amino-5-thio-1,2,4-triazole (3)

To 250 mL KOH (0.015 mol) abs. ethanol solution cinchophen hydrazide (0.01 mol) and CS_2 (0.015 mol) were added. The solution was stirred at room temperature for 24 h, then abs. ether (50 mL) was added to it and left as such for 2 h. The residue was filtered, washed (with ether and ethanol) and dried to give white solid potassium hydrazino dithioformate. This solid was dissolved in excess hydrazine hydrate (85%). The mixture was heated and refluxed for 6 h, cooled and poured into ice water (pH = 2 modulated by HCl) to give canary deposit which was filtered, dried and recrystallised from abs. ethanol. Yield 75%. MS: M^+ 319 (100), 229 (26); Anal. Calcd for $C_{17}H_{13}N_5S$: C, 63.95; H, 4.07; N, 21.94. Found: C, 64.05; H, 3.95; N, 21.65.

5-Cinchophenyl-1,2,4-triazolo[3,4-b]-1,2,3,4-thiatriazole (4)

The compound **3** (1.0 mmol) was stirred in sulphuric acid at 0-5 °C, then $NaNO_2$ (1.0 mmol) was added to it. Salt diazoate solution was added to the mixture of NaOAc ethanol solution (15 mg NaOAc dissolved in 10 mL ethanol) and acetyl methylene acetone. The resulting mixture was stirred for 10 min, filtered, washed and recrystallised from aqueous ethanol. IR (cm^{-1}) 3046 (m, υ_{ArH}); 1598 (s, $\upsilon_{C=N}$); 1239 (s, $\upsilon_{N-N=C}$); 693 (s, υ_{N-C-N}); ^1H NMR δ (ppm): 7.51-9.10 (m, 10H); Anal. Calcd for $C_{17}H_{10}N_6S$: C, 61.82; H, 3.03; N, 25.45. Found: C, 61.64; H, 3.17; N, 24.98.

6-Aryl-3-cinchopheny-1,2,4-triazolo[3,4-b]-1,3,4-thiadizole (5a-j)

The compound **3** (1.0 mmole) was refluxed with aromatic acid (1.0 mmol) in $POCl_3$ (6.0 mL) for 4 h. The reaction mixture was cooled and poured into NaOH ice water solution, filtered, washed and dried. The crude product was recrys-

tallised from DMF. The elemental analysis, ^{1}H NMR, IR and MS data of compound **5a-j** are respectively listed in Table 1, Table 2 and Table 3.

1-Cinchophenyamino-5-phenylcarbamide (6)

Cinchopheny hydrazide (10 mmol) was refluxed in abs. ethanol. When hydrazide was dissolved, an equal molar phenyl isocyanate was added into the solution that was refluxed for 3-4 h, cooled, filtered, washed and dried to give compound **6**. Yield 90%. mp 208-210 °C. Anal. Calcd for $C_{23}H_{18}N_4O$: C, 72.25; H, 4.71; N, 14.66. Found: C, 72.34; H, 4.84; N, 14.85.

Table 1. Physical Data and Elemental Analyses of Compounds **5a-j**

No.	Formula	Color	Yield	mp	Elemental anal. Found (Calcd.) (%)		
			(%)	(°C)	C	H	N
5a	$C_{24}H_{14}N_5SCl$	canary	73	303-305	65.66 (65.53)	3.09 (3.19)	15.95 (15.93)
5b	$C_{24}H_{14}N_5SF$	canary	81	278-280	68.16 (68.09)	3.22 (3.31)	16.87 (16.55)
5c	$C_{24}H_{14}N_5SI$	canary	84	313-315	54.07 (54.24)	2.56 (2.64)	13.41 (13.18)
5d	$C_{25}H_{17}N_5S$	yellow	82	299-301	70.89 (71.50)	3.94 (4.06)	16.86 (16.71)
5e	$C_{24}H_{14}N_5SBr$	canary	67	308-310	59.33 (59.50)	3.07 (2.89)	14.11 (14.46)
5f	$C_{24}H_{14}N_5SF$	yellow	79	218-220	67.80 (68.09)	3.40 (3.31)	16.71 (16.55)
5g	$C_{24}H_{14}N_5SCl$	canary	79	241-242	65.21 (65.53)	3.28 (3.19)	16.43 (16.71)
5h	$C_{25}H_{17}N_5S$	canary	80	223-224	71.34 (71.50)	4.04 (4.06)	17.04 (16.71)
5i	$C_{24}H_{14}N_5SBr$	canary	70	231-233	59.98 (59.50)	3.06 (2.89)	14.48 (14.46)
5j	$C_{24}H_{14}N_5SCl$	yellow	80	214-216	65.49 (65.53)	3.22 (3.19)	15.58 (15.93)

Table 2. ^{1}H NMR and IR Data of Compounds **5a-j**

Compd.	^{1}H NMR (ppm)	IR (cm^{-1})			
		ν_{ArH} (m)	$\nu_{C=N}$ (s)	$\nu_{N-N=C}$ (s)	ν_{C-S-C} (s)
5a	7.50-8.93 (m, 14H)	3037	1593	1237	687
5b	7.36-8.96 (m, 14H)	3034	1595	1236	687
5c	7.56-8.66 (m, 14H)	3033	1589	1237	688
5d	2.41 (s, 3H, CH_3) 7.49-8.89 (m, 14H)	3061	1591	1235	687
5e	7.73-8.86 (m, 14H)	3050	1589	1238	683
5f	7.40-8.87 (m, 14H)	3057	1591	1236	676
5g	7.43-8.93 (m, 14H)	3037	1597	1233	679
5h	2.42 (s, 3H, CH_3) 7.47-8.99 (m, 14H)	3040	1593	1285	689
5i	7.43-9.00 (m, 14H)	3055	1592	1239	686
5j	7.27-8.97 (m, 14H)	3033	1591	1237	683

Table 3. MS Data of Compounds **5a-i**

Compd.	*m/z* (relative abundance)
5a	439 (M^+, 100), 440 (M+1, 56), 402 (12), 229 (22).
5b	423 (M^+, 66), 424 (M+1, 19), 302 (24), 244 (12), 229 (62), 230 (25), 139 (100), 95 (10), 44 (26).
5c	531 (M^+, 55), 532 (M+1, 16), 404 (30), 302 (23), 247 (62), 230 (42), 229 (100), 203 (16), 202 (14), 120 (50), 26 (17), 44 (37).
5h	419 (M^+, 94), 418 (M-1, 79), 386 (15), 346 (11), 302 (24), 230 (28), 229 (68), 135 (100), 91 (18), 44 (34).
5i	483 (M^+, 35), 484 (M+1, 34), 404 (24), 302 (31), 230 (40), 229 (100), 201(20), 200 (51), 199 (43), 76 (16), 44 (18).

2-Arylamino-5-cinchopheny-1,3,4-oxadiazoline (7)

1-cinchophenoylamino-5-phenylcarbamide (**6**) (1.0 mmol) in $POCl_3$ (6.0 mL) was refluxed for 5 h, then the resulting mixture was poured into NaOH ice water solution resulting in much deposition that was filtered, washed, dried and recrystallised from aqueous ethanol to give compound **7**. mp 244-246 °C. Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.82; H, 4.40; N, 15.38. Found: C, 75.35; H, 4.68; N, 15.30.

ANTIBACTERAL AND ANTIFUNGAL ACTIVITY

The compounds **5b**, **5f** and **5g** were screened for their antibacterial activities in diluted agar media (50 ppm). Among the three compounds screened, **5g** (3-cinchopheny-6-(3-chlorophenyl)-s-triazolo[3,4-*b*]-1,3,4-thiadizole) exhibited antibacterial activities against *sclerotium blight of colza, gray mold of cucumber* and *cercospora brown spot of peanut*; the antibacterial rates respectively were 50.0%, 41.1% and 36.3%. If *o*, *m*- on 6-phenyl of compounds **5f** and **5b** were substituted by fluorine, their antibacterial rates changed to 0%, 29.4%, 27.2% and 0%, 41%, 27.2%. Could the conclusion be drawn that the antibacterial activity of 6-phenyl substituted by chlorine was better than that of fluorine? Though no rule could be drawn from the two compounds, the antibacterial rates of compound **5g** substituted by chlorine against three fungi were higher than those of compounds **5b** and **5f**. The biological activity of similar compounds is in the process of being screened and summarized.

ACKNOWLEDGEMENT

This work is supported by the National Natural Science Foundation of China and the Found of Ministry of Education of P. R. China.

Received March 31, 2003.

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