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A convenient synthesis of 3-arylsulfonyl -2,4(1H,3H)-quinazolinediones

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Abstract
A number of 3-arylsulfonyl- 2,4(1H,3H)-quinazolinediones were synthesized from 2-metoxycarbonylphenyl isocyanate and substituted arylsulfonamides in ethanol in the presence of potassium hydroxide.

Keywords: Monoester; Curtius rearrangement; Isocyanate; Arylsulfonamides; Quinazolinediones.

1. Introduction
The quinazoline and quinazolinedione nucleus were a very attractive and useful scaffold in medicinal chemistry: it can be found as a pharmacophore in a wide biologically active compounds, such as anticancer [1,2], anti-HIV [3], anti-inflammatory [4], antifungal [5], activities. Moreover, a variety of quinazolinediones is known to possess anticonvulsant, antioxidant [6], analgesic, diuretic and herbicide activities [7]. On the other hand, it has been reported that sulfonylureas and diarylsulfonylureas represent a new class of antitumor agents with a broad spectrum of activity [8-11]. Among the wide range of compounds tested as potential anticancer agents, derivatives comprising the sulfonamide and diarylsulfonylurea have attracted reasonable attention [12,13]. In particular, much interest has been given to the chemotherapeutic activity of quinazolinediones [14,15] and diarylsulfonylureas [16].
All these findings have promoted us to synthesize various sulfonylurea derivatives contain a quinazolinedione Skeleton in the hope to initiate a series of compounds which may appear more active. Thus it seemed of interest to study their combined effect when they occurred together in one molecule.

2. Materials and methods
Previous studies in our laboratory have reported that the reaction of α-amino acids with 2-carbomethoxyphenyl isocyanate give chiral 3-substituted-2,4(1H,3H)-quinazolinediones derivatives in which the nitrogen of the amino acid is incorporated into the fused pyrimidine ring [17] (Fig1). Our present aim was the synthesis of 3-arylsulfonyl-2,4(1H,3H)-quinazolinediones (1) compound in which is incorporated sulfonylureas and quinazolinedione skeleton.

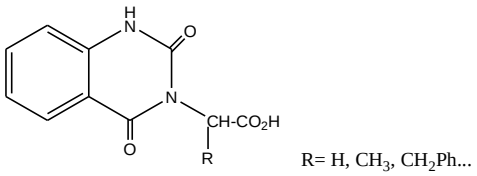
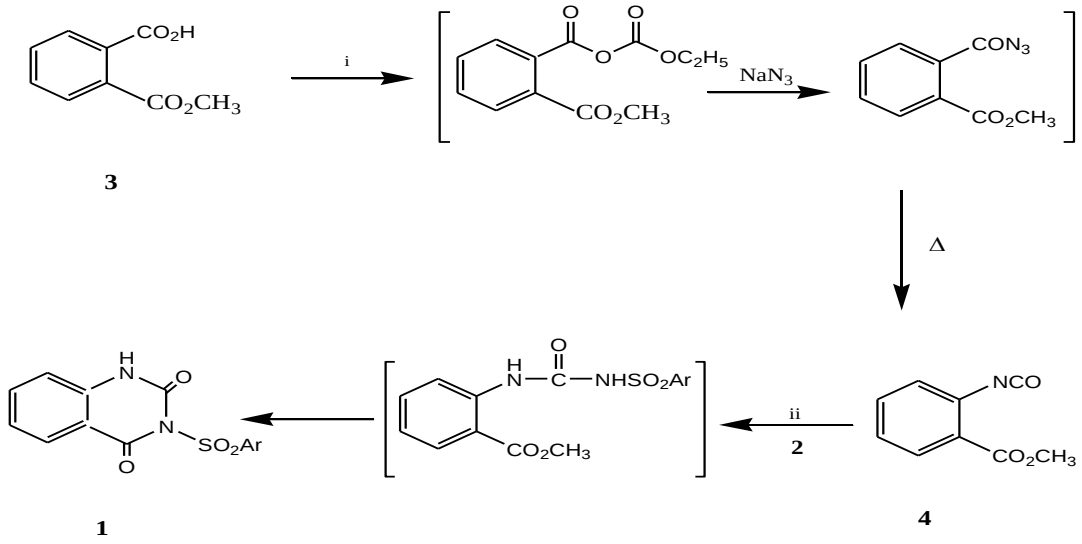


Fig 1: Synthesis of chiral 3-substituted-2,4(1H,3H)-quinazolinediones

3. Results and discussion
The reaction of the o-carbomethoxyphenyl isocyante(4) with arylsulfonamides (2) in ethanol in the presence of potassium hydroxyde affords (1) in good yields. The o-carbomethoxyphenyl isocyanate (4) was obtained from the monoester (3) via Curtius rearrangement [17] (Scheme 1).



i: $ClCO_2C_2H_5$ / $(C_2H_5)_3N$
ii: (2)= Ar-SO_2NH_2 ; KOH/C_2H_5OH

Scheme 1. Synthetic route of 3-Arylsulfonyl -2,4(1H,3H)-Quinazolinediones

The structure of the new quinazolinedione derivatives (1) were affirmed by their sharp melting point (mp) and spectral data (IR, ^{1}H NMR, and MS). The yields of the isolated compounds (1a-1f) are listed with constants in Table 1. As is shown in Table 1, we developed an efficient method for the preparation of various 3-arylsulfonyl-2,4(1H,3H)-quinazolinediones using an inexpensive starting material such as phtalic anhydride.

Experimental

Melting points were taken for samples in capillary tubes with an Electrothermal apparatus and are not corrected. The IR spectra were determined on a Shimadzu IR-435 instrument and the NMR spectra were recorded with Varian 300 (300MHz) spectrometers. Mass spectra were obtained using a VG-Instrument type Autospec-EQ.

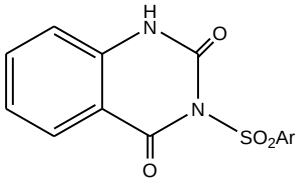
o-Carbomethoxyl phenyl isocyanate (4)

To a cold solution (-10°C) of half-ester (3) (1g, 5.55mmol) and triethylamine (1.55ml, 11.1 mmol) in tetrahydrofuran (15 ml) was added dropwise ethyl chloroformate (0.8 ml, 8.33 mmol) , and the resulting solution was stirred with ice cooling for 1h. Tlc analysis showed complete conversion to a non polar material. A solution of NaN_3 (0.9 g, 13.87 mmol) in H_2O (5.4ml) was then added dropwise with continued stirring for 1h. The reaction mixture was diluted with H_2O (50ml) and extracted with toluene (3 x 10ml). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated to a half volume in vacuum (to remove the tetrahydrofuran). The toluene solution was then slowly brought to reflux. After 1,5h, the yellow solution was isolated at room temperature and concentrated to 0.9 g (92%) of crude isocyante (4), which was used without purification. IR (neat) 2260, 1725 cm^{-1} ; 1H NMR ($CDCl_3$) _ 3.80 (s,3H), 7.35 (m, 2H), 7.70 (m,1H), 7.76(m,1H).

Synthesis of 3-Arylsulfonyl- 2,4(1H,3H)- Quinazolinediones (General procedure)

To a cold suspension (O°C) of arylsulfonamides (2) (5mmol), and powder KOH (0.56g, 10mmol) in anhydrous toluene (20ml), was added dropwise isocyanate (4) (0.9g, 5mmol) in absolute ethanol (5ml), and the resulting mixture was stirred at room temperature for 12h then refluxed for 24h. After cooling, the solvent was evaporated in vacuum. Water was added to the residue, filtered and acidified with hydrochloric acid (10%). The precipitate was collected by filtration and recrystallized from ethanol/ water to give the pure corresponding 3-Arylsulfonyl-2,4(1H,3H)-quinazolinediones.

Table 1: Physical properties, Yields and molecular formula of the synthesized compounds 1a-1f



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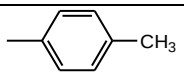
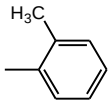
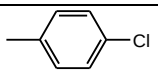
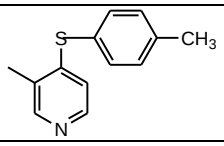
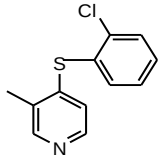
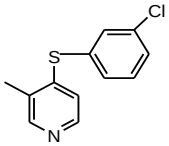
Coump. No	Ar	Yield %	MP.°C	Formula(Mol.Wt)	MS(m/z,FAB) $(M+H)^+$
(1a)		79	229-31	$C_{15}H_{12}N_2O_4S$ (316)	317
(1b)		75	218-21	$C_{15}H_{12}N_2O_4S$ (316)	317
(1c)		77	236-8	$C_{14}H_9N_2O_4SCl$ (336)	337
(1d)		70	257-9	$C_{20}H_{15}N_3O_4S_2$ (425)	426
(1e)		66	251-3	$C_{19}H_{12}N_3O_4S_2Cl$ (445)	446
(1f)		66	242-4	$C_{19}H_{12}N_3O_4S_2Cl$ (445)	446

3-(p-Toluene sulfonyl)-2,4 (1H,3H)- quinazolinedione (1a)

mp 229-31°C (ethanol/water 4/1) ; 79% yield ; IR(KBr, cm^{-1}) 3330, 1740,1695,1360,1180cm^{-1} ,^{1}H NMR (DMSO-D_6) _ 2.43(s ,3H, CH_3), 7.01(dd, J=8Hz, J=1.2Hz, 1H, ArH), 7.17(t, J=8Hz , 1H, ArH), 7.48(d, J=8Hz, 2H, ArH), 7.68(td, J=8Hz, J=1.2Hz, 1H, ArH), 7.88(dd, J=8Hz, J=1.2Hz, 1H, ArH), 8.02(d, J=8Hz, 2H, ArH), 11.50 (s, 1H, N-H) ; ^{13}C NMR (DMSO-d_6), ∂ (ppm): 21.18; 115.17; 115.55; 122.95; 127.62; 128.30; 129.60; 135.89; 139.26; 145.37; 147.29; 155.20; 161.15. MS (m/z, FAB) 317$(M+H)^+$, MS (EI, 70ev) (m/z, %) 316 (6.4, M^+), 252(66.1); 162(5.4); 146(46.4); 119(65); 91(100).

3-(O-Toluene sulfonyl)-2,4 (1H,3H)-quinazolinedione (1b)

mp 219-21°C (ethanol / water 4/1); 75% yield; IR (KBr, cm^{-1}) 3360, 1730, 1685, 1340, 1180 cm^{-1}; ^{1}H NMR (DMSO-D_6)_ 2.65(s, 3H, CH_3), 7.24(d, J=8.1Hz, 1H, ArH), 7.31(t, J=8Hz, 1H, ArH), 7.51-7.61(m, 2H, ArH), 7.70-7.80(m, 2H, ArH), 7.96 (d, J=8Hz, 1H, ArH), 8.20 (d, J=8Hz, 1H, ArH), 11.53 (s, 1H, N-H) ; ^{13}C NMR (DMSO-d_6), ∂ (ppm): 19.12; 114.68; 115.54; 123.23; 126.53; 127.68; 128.01; 130.16; 132.54; 134.14; 139.19; 147.22; 160.58; 179.80. MS (m/z, FAB) 317$(M+H)^+$.

3-(p-Chlorobenzene sulfonyl)-2,4 (1H,3H)-quinazolinedione (1c)

mp 236-8°C (ethanol /water 4/1) ; 77% yield ; IR(KBr, cm^{-1}) 3340, 1745,1685,1345,1175 cm^{-1} ,^{1}H NMR (DMSO-D_6) _ 7.10(d, J=8.2Hz, 1H, ArH), 7.18(t, J=8.2Hz, 1H, ArH), 7.64(t, J=8.2Hz, 1H, ArH), 7.76(d, J=8.5Hz, 2H, ArH) 7.82(d, J=8.2Hz, 1H, ArH) 8.17(d, J=8.5Hz, 2H, ArH) , 11.57 (s, 1H, N-H) ; ^{13}C NMR (DMSO-d_6), ∂ (ppm): 115.20; 115.49; 123.02; 127.64; 129.34; 130.24; 135.93; 139.09; 139.58; 147.26; 160.65; 161.62. MS (m/z, FAB) 337$(M+H)^+$.

3-[(p-Toluene thío) pyridine 3-sulfonyl]-2,4 (1H,3H)-quinazolinedione (1d)
mp 257-9°C (ethanol/water 4/1) ; 70% yield ; IR(KBr, cm^{-1}) 3340, 1740,1680,1350,1165 cm^{-1} ,^{1}H NMR (DMSO-D_6) _ 2.25 (s, 3H, CH_3), 6.86 (d, J=5.5Hz, 1H, ArH), 7.25(m, 3H, ArH), 7.40 (m, 3H, ArH), 7.86 (t, J=7.9Hz, 1H, ArH) , 8.05 (d, J=8Hz, 1H, ArH), 8.66(d, J=5.5Hz, 1H, ArH), 9.12 (s,1H, ArH), 10.55(s, 1H, N-H) ; ^{13}C NMR (DMSO-d_6), ∂ (ppm): 20.79; 114.67; 115.59; 121.34; 123.28; 127.77; 131.26; 135.30; 136.20;139.29; 141.13; 147.03;150.07; 150.58; 153.19; 160.29; 184.12;186.05. MS (m/z, FAB) 426 $(M+H)^+$; MS (EI,70ev) (m/z,%) 425 (27.5, M^+), 361(13.3); 306 (9.5); 264 (13.5); 162(100); 146(21.8); 119(99.1); 91(84.1).

3-[4-(O-Chlorophenyl thío) pyridine 3-sulfonyl]-2,4 (1H,3H)-quinazolinedione (1e)
mp 251-3°C (ethanol /water 4/1) ; 66% yield ; IR(KBr, cm^{-1}) 3360, 1735,1685,1350,1170 cm^{-1} ; ^{1}H NMR (DMSO-D_6) _ 6.89(d, J =5.5Hz, 1H, ArH), 7.25(d, J= 8.1Hz, 1H, ArH), 7.34(m, 3H, ArH), 7.41(d, J=5.5Hz, 2H, ArH), 7.65(d, J=8.1 Hz, 2H, ArH), 7.81(t, J=7.9Hz,1H, ArH), 9.22(s, 1H, ArH),11.80 (s,1H, N-H) ;MS (m/z, FAB) 446 $(M+H)^+$; MS (EI,70ev) (m/z,%) 445 (3.1, M^+), 238 (39.1); 221 (44.7); 162(100); 146(21.3); 119(94.1); 91(39.4).

3-[4-(m-Chlorophenyl thío) pyridine 3-sulfonyl]-2,4 (1H,3H)-quinazolinedione (1f)
mp 242-4°C (ethanol/water 4/1) ; 66% yield ; IR(KBr, cm^{-1}) 3340, 1735,1690,1340,1170 cm^{-1} ; ^{1}H NMR (DMSO-D_6) _ 6.91(d, J=5.5Hz, 1H, ArH), 7.26(d, J=8.1Hz, 1H, ArH), 7.34(t, J=8Hz, 1H, ArH), 7.43(d, J=8 Hz, 2H, ArH), 7.67(d, J=8.1 Hz, 2H, ArH), 7.80(t, J=7.9Hz,1H, ArH), 8.0(d, J=8Hz, 1H, ArH), 8.56(d, J=5.5Hz,1H, ArH), 9.17(s,1H, ArH), 10.40 (s,1H, N-H) ;MS (m/z, FAB) 446 $(M+H)^+$.

Conclusion
In summary, the series of 3- Arylsulfonyl-2,4(1H,3H)-quinazolinediones derivatives were prepared in high yields and through a cheap and convenient multistep synthesis pathway. The analogues of these compounds have been tested for their antitumor cell lines [16].

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