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ORIGINAL PAPER

Facile synthesis of 3-substituted quinazoline-2,4-dione and 2,3-di-substituted quinazolinone derivatives

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3-Substituted quinazoline-2,4(1*H*,3*H*)-dione and 2,3-di-substituted quinazolineone derivatives attract considerable interest due to their pharmacological properties. In this paper, we report the synthesis of *N*-substituted-3-nitrophthalimide derivatives *II–III*, the reactions of phthalimide *III* with amines, hydrazines, and amino acid derivatives to synthesise a small library of 3-substituted-5-nitroquinazoline-2,4(1*H*,3*H*)-diones *IV–XIV* and 2,3-di-substituted-6-nitro-quinazolineones *XVIII–XIX*.

Keywords: 3-nitrophthalic acid anhydride, *N*-hydroxy-3-nitrophthalimide, *N*-sulphonyloxy-3-nitrophthalimide, 3-substitued quinazoline-2,4(1*H*,3*H*)-diones, 2,3-disubstituted quinazolinones

Introduction

The chemistry of heterocyclic compounds represents half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical and other bioactive products. 3-substituted quinazoline-2,4(1*H*,3*H*)-diones *IV–XIV* and 2,3-di-substituted quinazolineones *XVIII–XIX* are classes of fused heterocyeles that attract considerable interest (Katritzky & Rees, 1984) due to their diverse biological properties such as anticancer, anti-inflammatory (Connolly et al., 2005), selective α_1-adrenoreceptor antagonists (Jain et al., 2008), cytosolic phospholipase $A_2\alpha$-inhibitors (Kirincich, 2009), anti-convulsant, and anti-hypertensive activities (Connolly et al., 2005; Jain et al., 2008; Rivero et al., 2004, 2009; Li et al., 2009).

Various methods (of synthesis) and reactants have been used to synthesise these compounds (Connolly et al., 2005; Shiau et al., 1990; Li et al., 2009; Rivero et al., 2009). We used the reaction of the *O*-sulphonyl derivative of hydroxamic acid *III* with amine nucleophile under heating (Fahmy et al., 1977, 1978; Fahmy, 2006), involving the Lossen rearrangement (Sheradsky & Itzhak, 1986; Gütschow, 1999) to afford the desired compounds *IV–XIV* (Fig. 1) and compounds *XVIII–XIX* (Fig. 2). Their application to the de-activation of serine proteases has been investigated previously (Neumann & Gütschow, 1994; Martyn et al., 1999; Kerrigan et al., 2000; Vagnoni et al., 2001). Furthermore, the inhibitory activity of 3-substituted quinazoline-2,4(1*H*,3*H*)-dione derivatives towards puromycin-sensitive aminopeptidase has been studied as anti-angiogenesis agents in cancer treat-

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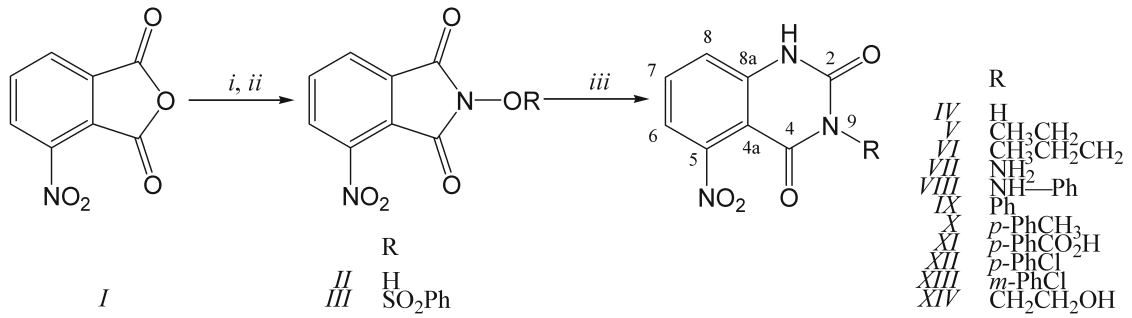

Fig. 1. Synthesis of 3-substituted quinazoline-2,4(1*H*,3*H*)-dione derivatives *IV*–*XVII*. Reaction conditions: *i*) $NH_2OH \cdot HCl$, pyridine, reflux, 30 min; *ii*) $PhOSO_2Cl$, –5 °C to 0 °C, diluted HCl; *iii*) –ammonia, absolute ethanol; –ethylamine/propylamine, fusion at 190 °C; –aniline, fusion at 190 °C; amines, toluene, reflux, 3 h.

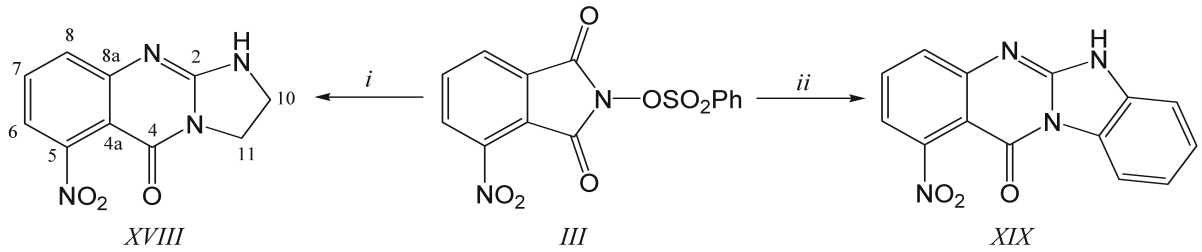

Fig. 2. Reaction of *N*-(phenylsulphonyloxy)phthalimide (*III*) with diamines: *i*) ethylenediamine, 180 °C; *ii*) *o*-phenylenediamine, fussion.

ment (Kakuta et al., 2003a, 2003b; Petrov & Andreev, 2005; Huang et al., 2009). Recently, a novel series of competitive AMPA receptor antagonists based on heterocyclic quinazolinedione scaffolds displaying high receptor affinity and oral in vivo activity was reported and developed (Koller et al., 2011; Orain et al., 2012).

In this paper, we introduce a facile synthetic pathway to synthesise 3-substituted quinazoline-2,4(1*H*, 3*H*)-diones *IV*–*XIV* and 2,3-di-substituted quinazolineones *XVIII*–*XIX* through the base-catalysed Lossen rearrangement reactions of *N*-(sulphonyloxy) phthalimide *III* with amines, hydrazines, and amino acid derivatives (Farouk, 2009, Farouk et al., 2012).

Experimental

3-Nitrophthalic anhydride and phthalic anhydride were prepared following the procedures described previously (Furniss et al., 1989). Anhydrous solvents were dried following the standard procedures (Perrin & Armarego, 1988). Hydrazine hydrate (60 %, Sigma–Aldrich, Germany) was used as reagent grade solution.

Melting points were determined with a Thermo Scientific Electrothermal IA9100 digital apparatus (Thermo Fisher Scientific, USA) and are uncorrected. For crystal structure determination, a suitable yellow block of compound (*III*) was selected under the optical microscope, glued and mounted onto a thin glass capillary. Diffraction data were collected using a Rigaku Raxis RAPID diffractometer (Rigaku, Japan) equipped with an imaging plate area detector using MoK_α radiation (λ = 0.71073 Å) with a graphite monochromator. The data were collected at a temperature of (294 ± 2) K to a maximum 20° of 55.0° using ω-scans with the crystal-to-detector distance of 127.40 mm for (*III*). Preliminary orientation matrices, unit cell determination, and data reduction were performed using the Crystal Clear package (Rigaku, Japan). The data were empirically corrected for absorption, Lorentz, and polarisation effects. Both structures were resolved by direct methods and refined by full-matrix least squares on all [F^2] data using SHELX packages (Sheldrick, Tubingen University, Germany). Hydrogen atoms were isotropically refined and constrained to ideal geometry using their appropriate riding model and all non-hydrogen atoms were anisotropically refined. Figures were created using the DIAMOND package (Brandburg. Diamond, Germany). Crystal data and refinement details are summarised in Table 1. The CIF file containing full information on structure *III* under study was deposited at the Cambridge Crystallographic Data Centre, CCDC and allocated deposition number: 797031. This information is available on request from the following website: www.ccdc.cam.ac.uk/. IR spectra were recorded on a Shimadzu 408 spectrometer (Shimadzu, Japan) using the KBr pellet technique. ^{1}H NMR (200 MHz, 400 MHz) and ^{13}C NMR (90 MHz, 100 MHz) spectra (in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard) were recorded using a Jeol Eclipse 400 spectrometer (Jeol, Japan). EI mass spectra were measured using a Hewlett–Packard (Agilent, Japan)

Table 1. Crystal data and refinement details for compound *III*

Identification code	Compound *III*
Formula	$C_{14}H_8N_2O_7S$
Formula mass	348.29
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	$A = 7.9176(18)$ Å, $\alpha = 70.398(5)°$ $B = 8.1638(17)$ Å, $\beta = 76.129(6)°$ $C = 12.382(3)$ Å, $\gamma = 84.870(6)°$
V/Å^3	731.9(3)
Z	4
Density (calculated)/(kg m^{-3})	1580
Crystal size/mm	0.20 × 0.50 × 0.55 (yellow blocks)
Temperature/K	293
Radiation (MoK_α)/Å	0.71075
θ_{min}, θ_{max}/°	3.5, 27.5
Dataset	–10 : 10; –10 : 10; –16 : 16
Total data	17485, 3336, 0.036
Observed data	2784
N_{ref}, N_{par}	3336, 218
R, w_{R2}, S	0.0382, 0.1064, 1.02
Minimum and maximum residual density/(e Å^{-3})	–0.31, 0.24

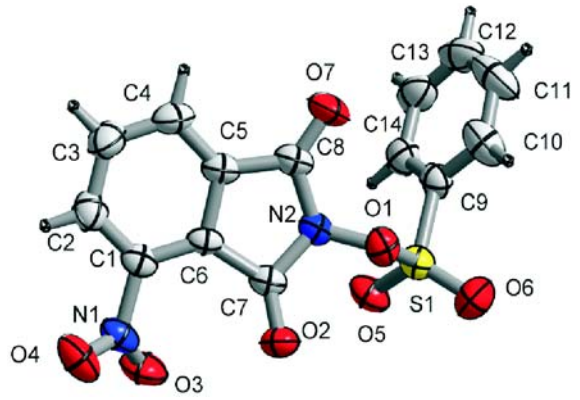

Fig. 3. ORTEP drawing of compound (*III*).

5988A GC/MS system at ionisation energy of 70 eV. Tables 2 and 3 presents characterization data of newly synthesized compounds *III*–*IV*, *VIII*–*XIX*.

N-phenylsulphonyloxy-3-nitrophthalimide (III)

A mixture of nitrophthalic anhydride *I* (3 g, 18.0 mmol), hydroxylamine hydrochloride (1.51 g, 23.3 mmol), and dry pyridine (5 mL) was heated under reflux for 30 min. Benzenesulphonyl chloride (2.8 g, 15.9 mmol) was then added to the reaction mixture at –5 ℃ to 0 ℃ and the reaction mixture was stirred at this temperature for 15 min, followed by the addition of a cold diluted HCl–H_2O solution ($\varphi_r = 1 : 1$). The precipitate thus formed was filtered, dried, and crystallised from toluene to afford *III* (3.6 g) as pale yellow crystals. The X-ray analysis is shown in Fig. 3.

Synthesis of 5-nitroquinazoline-2,4(1H,3H)-dione (IV)

When dry ammonia gas was allowed to pass through a suspension of phthalimide *III* (0.5 g, 1.44 mmol) in absolute ethanol (5 mL), a clear solution was obtained after 1 h. The solvent was removed under reduced pressure and the solid thus formed was washed with ethanol, dried, and crystallised from ethanol to give *IV* (0.28 g).

General procedure for synthesis of 3-alkyl-5-nitroquinazoline-2,4(1H,3H)-diones (V–VI)

A mixture of phthalimide *III* (0.35 g, 1 mmol) and alkylamine (3.0 mmol), namely ethylamine and propylamine, was heated at 190 ℃ under vacuum in a sublimation apparatus for 1 h. Under reduced pressure, the solid volatilises and condenses on a cold finger as a purified compound *V* (3-ethyl-5-nitroquinazoline-2,4(1*H*,3*H*)-dione) and *VI* (3-propyl-5-nitroquinazoline-2,4(1*H*,3*H*)-dione) with yield of 0.19 g and 0.21 g, respectively.

Synthesis of 3-amino-5-nitroquinazoline-2,4(1H,3H)-dione (VII)

A mixture of phthalimide *III* (0.5 g, 1.44 mmol) and hydrazine hydrate (0.14 g, 2.15 mmol) was heated under reflux in toluene (10 mL) for 2 h. The solid formed after cooling was filtered, washed with ethanol, dried, and crystallised from ethanol to give *VII* (0.29 g).

Table 2. Characterisation data of newly prepared compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.
			C	H	N	S	%	℃
III	$C_{14}H_8N_2O_7S$	348.29	48.28	2.31	8.04	9.20	67	176–178
			48.60	2.52	8.34	9.28		
IV	$C_8H_5N_3O_4$	207.14	46.39	2.43	20.29		93	329–331
			46.50	2.18	20.21			
V	$C_{10}H_9N_3O_4$	235.20	51.07	3.86	17.88		83	253–255
			51.11	3.59	17.62			
VI	$C_{11}H_{11}N_3O_4$	249.22	53.02	4.45	16.78		85	246–248
			53.21	4.49	16.72			
VII	$C_8H_6N_4O_4$	222.16	43.25	2.72	25.22		94	258–260
			43.53	2.61	25.39			
VIII	$C_{14}H_{10}N_4O_4$	298.25	56.38	3.38	18.78		81	238–240
			56.61	3.22	18.85			
IX	$C_{14}H_9N_3O_4$	283.24	59.37	3.20	14.84		76	236–238
			59.68	2.27	14.70			
X	$C_{15}H_{11}N_3O_4$	297.27	60.61	3.73	14.14		65	283–285
			60.35	3.90	14.15			
XI	$C_{15}H_9N_3O_6$	327.25	55.05	2.77	12.84		69	358–360
			55.29	2.49	12.62			
XII	$C_{14}H_8ClN_3O_4$	317.68	52.93	2.54	13.23		76	283–285
			52.97	2.74	13.11			
XIII	$C_{14}H_8ClN_3O_4$	317.68	52.93	2.54	13.23		87	228–230
			52.95	2.33	13.67			
XIV	$C_{10}H_9N_3O_5$	251.20	47.81	3.61	16.73		69	240–242
			47.77	3.66	16.68			
XVIII	$C_{10}H_8N_4O_3$	232.20	51.73	3.47	24.13		75	295–297
			51.44	3.44	24.08			
XIX	$C_{14}H_8N_4O_3$	280.24	60.00	2.88	19.99		60	296–298
			60.28	2.85	20.40			

Synthesis of 3-(anilino)-5-nitroquinazoline-2,4(1H,3H)-dione (VIII)

A mixture of phthalimide *III* (0.5 g, 1.44 mmol) and excess of phenylhydrazine (0.4 mL, 4.32 mmol) in toluene (10 mL) was heated under reflux for about 2 h. The yellow crystals formed after cooling were filtered, washed with methanol, and recrystallised from methanol to give *VIII* (0.35 g).

Synthesis of 5-nitro-3-phenylquinazoline-2,4(1H,3H)-diones (IX)

A mixture of phthalimide *III* (0.35 g, 1 mmol) and aniline (3 mmol) was heated at 190℃ under vacuum in a sublimation apparatus for 1 h. Under reduced pressure, the solid volatilises and condenses on a cold finger as a purified compound *IX* (0.23 g).

General procedure for synthesis of 3-aryl-5-nitroquinazoline-2,4(1H,3H)-dione (X–XIII)

A mixture of phthalimide *III* (0.35 g, 1 mmol) and aromatic amines, namely *p*-toludine, *p*-aminobenzoic acid, *p*-chloroaniline, and *m*-chloroaniline (3 mmol) in 10 mL of dry toluene, was heated under reflux for 2 h. After cooling, the solid thus formed was filtered, washed with ethanol and crystallised from the appropriate solvents to afford the substituted aniline 3-aryl-5-nitroquinazoline-2,4(1H,3H)-diones *X–XIII*: 3-(4-methylphenyl)-5-nitroquinazoline-2,4(1*H*,3*H*)-dione (*X*, 0.2 g), 4-[5-nitro-2,4-dioxo-1,2-dihydroquinazolin-3(4H)-yl]benzoic acid (*XI*, 0.23 g), 3-(4-chlorophenyl)-5-nitroquinazoline-2,4(1*H*,3*H*)-dione (*XII*, 0.24 g), and 3-(3-chlorophenyl)-5-nitroquinazoline-2,4(1*H*,3*H*)-dione (*XII*, 0.28 g).

Synthesis of 3-(2-hydroxyethyl)-5-nitroquinazoline-2,4(1H,3H)-dione (XIV)

A mixture of (0.5 g, 1.44 mmol) phthalimide *III* and ethanol amine (0.1 g, 2.15 mmol) in dry toluene (10 mL) was heated under reflux for 2 h. The solvent was removed after cooling under reduced pressure. The remaining solid was washed with methanol and then crystallised from ethanol to give *XIV* (0.25 g).

Table 3. Spectral data of newly prepared compounds

Compound	Spectral data
III	IR, $\tilde{\nu}$/cm^{-1}: 1205 (S═O), 1350, 1540 (N═0), 1750, 1810 (C═O) ^{1}H NMR (DMSO-d_6), δ: 7.64 (t, 2H, J = 7.7 Hz, H_{aryl}), 7.80 (t, 1H, J = 7.3 Hz, H_{aryl}), 8.01 (t, 1H, J = 7.7 Hz, H_{aryl}), 8.10 (d, 2H, J = 7.36 Hz, H_{aryl}), 8.20 (dd, 2H, J = 8.04 Hz, H_{aryl}) MS, m/z (I_r/%): 348 (46) (M^+)
IV	IR, $\tilde{\nu}$/cm^{-1}: 1695, 1745 (C═O), 3100, 3500 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.50 (m, 1 H, H_{aryl}), 7.80 (m, 1 H, H_{aryl}), 8.20 (s, 1 H, NH), 8.34 (d, 1H, J = 8.2, H_{aryl}), 11.40 (broad, 1H, NH) MS, m/z (I_r/%): 207 (36) (M^+)
V	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1680, 1740 (C═O), 3180, 3200 (NH) ^{1}H NMR (DMSO-d_6), δ: 1.13 (t, 3H, J = 7.2 Hz, CH3), 3.89 (q, 2H, J = 7.0 Hz, CH_2), 7.37 (d, 1H, J = 8.4 Hz, H_{aryl}), 7.47 (d, 1H, J = 7.8 Hz, H_{aryl}), 7.81 (t, 1H, J = 7.9 Hz, H_{aryl}), 11.87 (s, 1H, NH)
VI	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1680, 1740 (C═O), 3180, 3200 (NH) ^{1}H NMR (DMSO-d_6), δ: 0.87 (t, 3H, J = 7.4 Hz, CH_3), 1.57 (m, 2H, CH_2), 3.79 (t, 2H, J = 7.7 Hz, CH_2), 7.36 (d, 1H, J = 8.2 Hz, H_{aryl}), 7.45 (d, 1H, J = 7.0 Hz, H_{aryl}), 7.81 (t, 1H, J = 8.1 Hz, H_{aryl}), 11.91 (s, 1H, NH) ^{13}C NMR (DMSO-d_6), δ: 12.50 (C-11), 14.30 (C-10), 32.45 (C-9), 120.07 (C-4a), 125.55 (C-6), 127.82 (C-8), 130.89 (C-7), 137.32 (C-8a), 146.08 (C-5), 164.94 (C-2), 165.87 (C-4)
VII	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1640, 1740 (C═O), 3250, 3360 (NH_2), 3490 (NH) ^{1}H NMR (DMSO-d_6), δ: 5.36 (s, 2H, NH_2), 6.25 (d, 1H, J = 7.8 Hz, H_{aryl}), 6.83 (d, 1H, J = 8.2 Hz, H_{aryl}), 7.34 (t, 1H, J = 8.1 Hz, H_{aryl}), 9.10 (s, 1H, NH)
VIII	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1680, 1740 (C═O), 3300–3400 (NH) ^{1}H NMR (DMSO-d_6), δ: 6.80 (m, 3H, H_{aryl}), 7.12 (t, 1H, J = 7.8 Hz, H_{aryl}), 7.47 (t, 1H, J = 8.1 Hz, H_{aryl}), 8.42 (dd, 1H, J = 7.8 Hz, H_{aryl}), 8.54 (dd, 1H, J = 8.3 Hz, H_{aryl}), 8.68 (s, 1H, NHPh), 10.83 (s, 1H, CONH)
IX	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1670, 1740 (C═O), 3180 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.11 (m, 1H, H_{aryl}), 7.34 (m, 2H, H_{aryl}), 7.58 (d, 1H, J = 8.6 Hz, H_{aryl}), 7.66 (d, 1H, J = 8.4 Hz, H_{aryl}), 7.85 (t, 1H, J = 8.0 Hz, H_{aryl}), 8.11 (d, 1H, J = 7.7 Hz, H_{aryl}), 8.30 (d, 1H, J = 8.4 Hz, H_{aryl}), 10.62 (s, 1H, NH) ^{13}C NMR (DMSO-d_6), δ: 120.18 (C-10), 120.44 (C-4a), 124.26 (C-6), 124.54 (C-8), 126.23 (C-13), 129.28 (C-11), 130.85 (C-12), 132.26 (C-10), 133.82 (C-14), 138.11 (C-9), 139.35 (C-7), 139.47 (C-8a), 147.26 (C-5), 163.19 (C-4), 165.13 (C-2)
X	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1620, 1750 (C═O), 3100–3400 (NH) ^{1}H NMR (DMSO-d_6), δ: 2.39 (s, 3H, CH_3), 6.96 (t, 1H, J = 8.4 Hz, H_{aryl}), 7.20 (m, 4H, H_{aryl}), 7.47 (t, 1H, J = 7.8 Hz, H_{aryl}), 7.70 (d, 1H, J = 7.4 Hz, H_{aryl}), 8.10 (d, 1H, J = 7.8 Hz, H_{aryl}), 10.16 (s, 1H, NH)
XI	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1620, 1750 (C═O), 3100–3400 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.50 (m, 3H, H_{aryl}), 8.10 (m, 2H, H_{aryl}), 8.40 (dd, 1H, J = 7.8 Hz, H_{aryl}), 8.50 (dd, 1H, J = 8.2 Hz, H_{aryl}), 10.65 (s, 1H, NH), 13.00 (broad s, 1H, COOH)
XII	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1620, 1750 (C═O), 3100–3400 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.48 (m, 6H, H_{aryl}), 7.95 (d, 1H, J = 7.2 Hz, H_{aryl}), 11.62 (s, 1H, NH)
XIII	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1620, 1750 (C═O), 3100–3400 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.04 (d, 1H, J = 7.6 Hz, H_{aryl}), 7.36 (m, 3H, H_{aryl}), 7.72 (t, 1H, J = 8.6 Hz, H_{aryl}), 7.95 (d, 1H, J = 9 Hz, H_{aryl}), 8.37 (d, 1H, J = 8.4 Hz, H_{aryl}), 11.00 (s, 1H, NH)
XIV	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1640, 1710 (C═O), 3400 (NH), 3550 (OH) ^{1}H NMR (DMSO-d_6) δ: 3.95 (t, 2H, J = 6.4 Hz, CH_2), 4.76 (t, 2H, J = 6.0 Hz, CH_2), 4.84 (t, 2H, J = 5.4 Hz, CH_2), 4.87 (t, 1H, J = 5.2 Hz, OH), 6.27 (dd, 1H, J = 8.3 Hz, H_{aryl}), 7.35 (t, 1H, J = 8.2 Hz, H_{aryl}), 8.70 (d, 1H, H_{aryl}), 11.09 (s, 1H, NH) ^{13}C NMR (DMSO-d_6), δ: 40.6 (C-9), 58.33 (C-10), 58.89 (C-4a), 100.44 (C-6), 103.51 (C-8), 136.12 (C-7), 140.18 (C-8a), 151.01 (C-5), 152.20 (C-2), 165.20 (C-4)
XVIII	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1645 (C═N), 1700 (C═O), 3490 (NH) ^{1}H NMR (DMSO-d_6), δ: 3.87 (m, 4H, $2CH_2$), 7.01 (d, 1H, J = 7.8 Hz, H_{aryl}), 7.50 (t, J = 7.8 Hz, 1H, H_{aryl}), 7.78 (d, 1H, J = 7.8 Hz, H_{aryl}), 10.20 (broad s, 1H, NH) ^{13}C NMR (DMSO-d_6), δ: 40.44 (C-11), 49.27 (C-10), 49.55 (C-8), 54.49 (C-6), 58.00 (C-4a), 126.04 (C-7), 128.29 (C-5), 129.25 (C-8a), 148.31 (C-2), 172.79 (C-4)
XIX	IR (KBr), $\tilde{\nu}$/cm^{-1}: 1610 (C═N), 1650 (C═O), 3290 (NH) ^{1}H NMR (DMSO-d_6), δ: 7.66 (m, 6H, H_{aryl}), 8.40 (t, 1H, J = 4.4 Hz, H_{aryl}), 12.39 (s, 1H, NH)

Synthesis of 6-nitro-2,3-dihydroimidazo[2,1-b] quinazolin-5(1H)-one (XVIII)

A mixture of phthalimide *III* (0.5 g, 1.44 mmol) and excess of ethylenediamine (0.3 ml, 4.32 mmol) was heated at 190 ℃ in an oil bath. The solid product thus formed was washed several times with petroleum ether at 40–60 ℃ and then with methanol, crystallised from petroleum ether–methanol (40–60 ℃) to afford *XVIII* (0.24 g).

Synthesis of 1-nitrobenzo[4,5]imidazo[2,1-b] quinazolin-12(6H)-one (XIX)

A mixture of phthalimide *III* (0.5 g, 1.44 mmol) and *O*-phenylenediamine (0.23 g, 2.15 mmol) was heated at 190 °C under vacuum in a sublimation apparatus for 1 h. Under reduced pressure, the solid volatilises and condenses on a cold finger as a purified compound *XIX* (0.28 g).

Results and discussion

The sequence of syntheses of compounds (*I–XIV*) is shown in Fig. 1. Hydroxylamine hydrochloride was allowed to react with anhydrides *I* in dry pyridine under reflux to give the corresponding oxime *II*. These were, without isolation, treated with benzenesulphonyl chloride to give compound *III* with a 67 % yield. The IR spectra of *III* showed the expected two bands corresponding to the carbonyl groups of cyclic imides (Fahmy et al., 1977, 1978; Fahmy, 2006; Fieser & Fieser, 1967); the X-ray structure analysis determined the chemical constituent of compound *III* (Fig. 3).

Ammonolysis of sulphonyloxy derivative *III* with dry ammonia at ambient temperature afforded compound *IV* with a 93 % yield. The IR bands of *IV* showed different bonds for υ(NH) in the region of 3500–3100 cm^{-1} and for ν(C═O) at 1745 cm^{-1} and 1695 cm^{-1}. ^{1}H NMR data confirmed the structure of compounds *IV*.

The presence of the nitro group may be due to an initial attack of the amine on the carbonyl in the *ortho* (not *meta*) position relative to the nitro group in *III*. Consequently, after ring opening, the Lossen rearrangement would occur at the substituent in the *meta* position, thus leading to the 3-substituted-5-nitroquinazoline-2,4(1*H*,3*H*)-diones *IV–XIV*.

The fusion of compound *III* with aliphatic amines, namely ethylamine and propylamine, at 190 °C under vacuum afforded the desired 3-alkyl-quinazoline-2,4(1*H*,3*H*)-dione substituted derivatives *V* and *VI* with yields of 83 % and 85 %, respectively. The adsorption bands at 3180 cm^{-1} and 3200 cm^{-1} for both compounds *V* and *VI* (see also Koay and Campeau (2011)) were attributed to the N—H stretching vibration of the secondary amine group. ^{1}H NMR and ^{13}C NMR data confirmed the structure of compounds *V* and *VI*.

Hydrazinolysis of phthalimide*III* with hydrazine hydrate and phenyl hydrazine in refluxing dry toluene afforded 3-substituted quinazoline-2,4-diones *VII* and *VIII* with yields of 94 % and 81 % respectively. The IR spectrum of *VII* revealed absorption bands at 3250 cm^{-1} and 3360 cm^{-1} corresponding to the N—H stretching vibration of the primary amine group, the absorption band at 3490 cm^{-1} corresponding to the N—H stretching vibration of the secondary amine group. For compound *VIII,* the IR spectrum showed absorption bands at 3300 cm^{-1} and 3400 cm^{-1} corresponding to the N—H stretching vibration of the secondary amine groups. ^{1}H NMR data confirmed the structure of compounds *VII* and *VIII.*

The treatment of phthalimide*III* with aromatic amines, namely *p*-toluidine, *p*-chloroaniline, *m*-chloroaniline, and *p*-aminobenzoic acid, in dry toluene under reflux afforded the 3-substituted derivatives *XI–XV* with good yields; the desired compound *X* was obtained with a 76 % yield when phthalimide *III* was fused with aniline at 190 °C under vacuum.

Ethanolamine reacted with compound *III* in dry toluene under reflux; the sole product formed was derivative *XVII* with a 69 % yield; this was consistent with its analytical spectral data observed.

When compound *III* was allowed to react with bi-functional amines, namely ethylene diamine and *O*-phenylendiamine, 2,3-disubstituted quinazolinones *XX* and *XXI* were obtained with 78 % and 72 % yields respectively. The chemical structures of compounds *XX* and *XXI* were elucidated from their analytical spectral data.

Conclusion

N-phenylsulphonyloxy-3-nitrophthalimide *III* was synthesised with a good yield as key intermediate compound; its chemical structure was confirmed by NMR, IR, and X-ray analysis. In one-vessel synthetic reactions, 3-substituted quinazoline-2,4(1*H*,3*H*)-dione and 2,3-di-substituted quinazolinones derivatives were synthesised affording moderate to high yields via the reaction of *III* with the ammonia, amino acid, amines, and hydrazines.

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