Synthesis and screening of quinolone antibiotic isosteres

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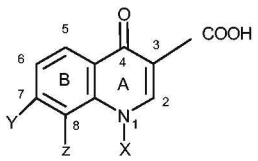
Condensation of either 4-(benzothiazol-2-yl)phenylamine **1** or 4-amino-2-(benzothiazol-2-yl)-phenol **2** with ethyl cyanoethoxyacrylate or diethyl ethoxymethylenemalonate (EMME) followed by intra molecular thermal cyclisation results in substituted quinolones which upon alkylation then base-hydrolysis yielded the target compounds 6-(benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **(3a,b)**; 7-(benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydro-6-alkoxyquinoline-3-carboxylic acid **(4a,b)**. Meanwhile diazotisation of 4-(benzothiazol-2-yl)phenylamine **(1)** followed by reaction with malononitrile then intra molecular Friedel-Crafts acylation gave 4-amino-6-(benzothiazol-2-yl)cinnoline-3-carbonitrlie **5**. The antimicrobial activity of some of the target compounds using gram-positive microbes (*Staphylococcus aureus* and *Bacillus subtilis*) and gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) is carried out and 6-(benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydro quinoline-3-carboxylic acid **(3a,b)** and 7-(benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydro-6-alkoxyquinoline-3-carboxylic acid **(4a,b)** showed promising activity.

Keywords: quinolones, benzothiazoles, isosteres, pyridinone carboxylic acid, antibiotics

Quinolones are very promising class of antibiotics since they have been proved to exhibit broad spectrum, potent activity and good pharmacokinetics properties. Many clinically important antibacterial agents having a quinolone moiety and collectively known as quinolones have been discovered. Modification of the groups which occupy the N-1, C-7 and C-8 positions has been successful in yielding potent antibacterial agents Fig. 1.[1,2]



The structure–activity relationship studies concluded that, for optimal antimicrobial activity of any quinolone antibiotics position 1 should have either a methyl or an ethyl group or its bioisosteres such as fluoroethyl, methylamino, methoxy *etc*. while position 2 requires a hydrogen atom for maximum antimicrobial potency. Positions 3 and 4 are a link between the carboxylic acid group and the keto group, and are generally considered necessary for binding of quinolones to DNA gyrase.[1,3] Classical studies have produced no active quinolones with a significant modification of the C-3 carboxylic acid group. For position 4, it has been extensively explored, and replacement of the 4-keto group with other groups so far has led to inactive compounds. Of the various C-6 substituents (H, F, Cl, Br, CH_3, SCH_3, $COCH_3$, CN and NO_2), the addition of a fluorine atom resulted in a dramatic increase in antibacterial potency.[1] The "medium size" concept concerning the 7-substituents is no longer valid. Numerous potent quinolones with a large group at position 7 have been discovered. A certain amount of free rotation in the position 7-substituents appears to emerge as an important factor which influences the activity of the compounds.[2] The objective of this work is to synthesise compounds that are a combination between quinolone nucleus and another highly antimicrobial nucleus, *e.g.* benzothiazole moiety, to evaluate the activity and whether a synergistic effect will occur or there is no pronounced change in the activity.

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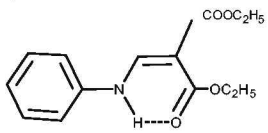
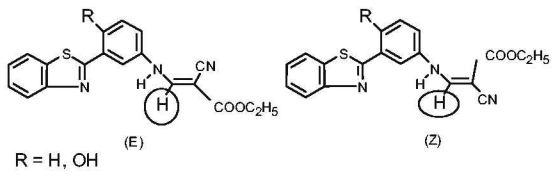
Results and discussion

Synthesis of the target compounds **3–5** is illustrated in Scheme 1. This shows preparation of the aminophenyl-benzothiazoles **1** and **2** is via cyclodehydration reaction between 2-aminothiophenol and either 4-aminobenzoic acid (PABA) or 5-aminosalicylic acid sequentially using polyphosphoric acid (PPA) as a dehydrating agent. Several dehydrating agents have been reported, however, PPA is the reagent of choice since it documented that it gave good yield[4-11] and this is the procedure that was adapted herein.[11] Reaction of compounds **1** and **2** with either ethyl cyanoethoxyacrylate or diethyl ethoxymethylenemalonate in refluxing ethanol is through Michael addition followed by elimination of ethanol[12-14] to give rise to two geometrical isomers ***(ZE)*** in nearly equimolar amounts, so there is no significant steric effect between the two isomers.

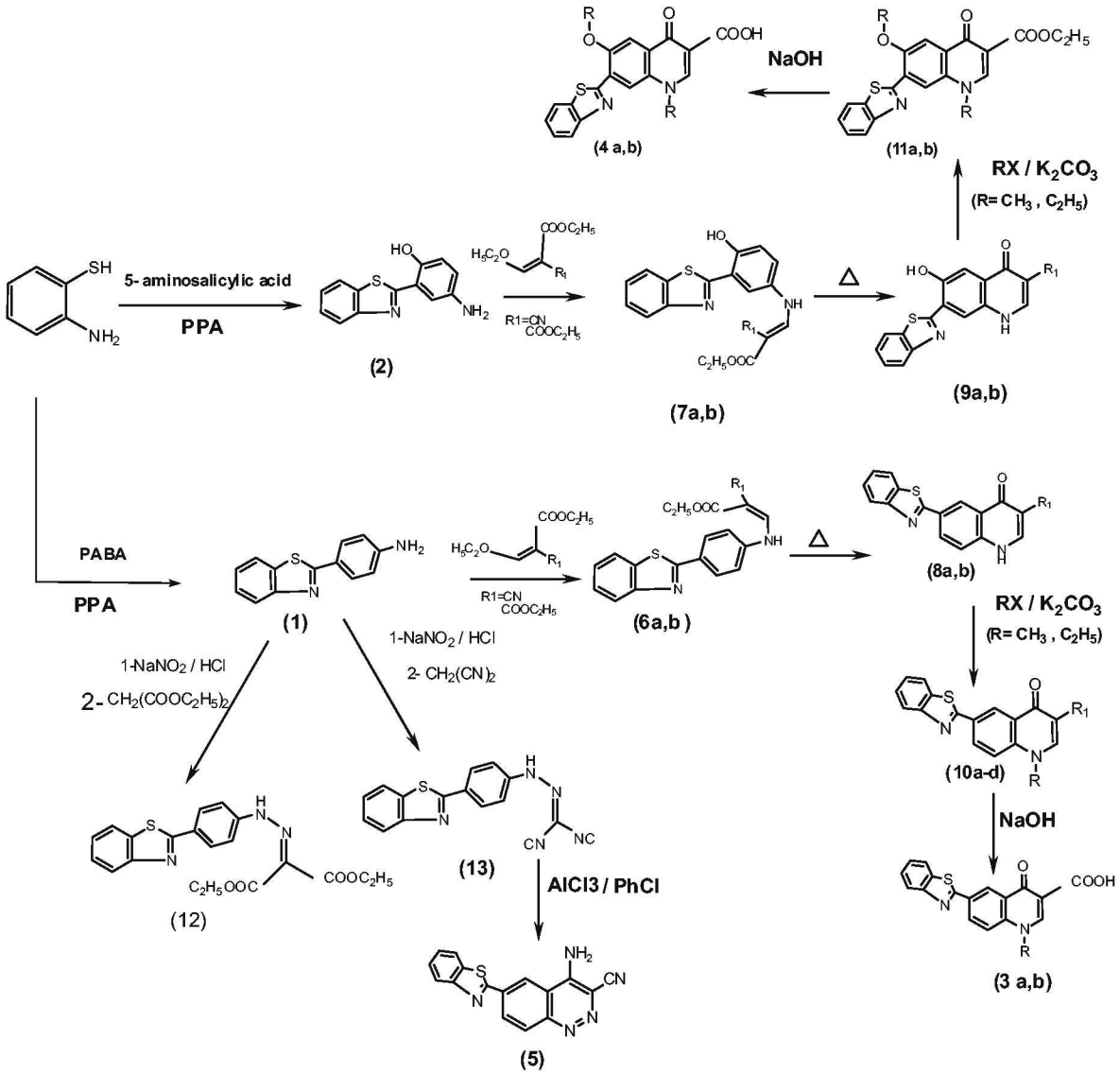
The IR spectra of compounds **6b** and **7b** showed two values of the carbonyl of the two ester groups and this may be attributed to the formation of intra molecular hydrogen bond as shown in Fig. 2.



Examination of ^{1}H NMR spectrum of compounds **6a** and **7a** suggested the presence of two geometrical isomers ***(ZE)*** Fig. 3. This was indicated by the appearance of two single peaks each equal to 0.5 proton and do not disappear after D_2O addition at δ 8.42 and 8.62 ppm (2 s, 0.5H, C***H***=C). In the case of compounds **6b** and **7b** there is a doublet signal at δ 8.48 ppm for C***H***=C. This is due to the exchange of the N***H*** proton which was coupled with C***H***=C.



Compounds **6a,b** and **7a,b** were exposed to intra molecular cycloacylation reaction in a high boiling point solvent–diphenyl ether- to yield the unalkylated 4-quinolones **8a,b** and



Scheme 1

9a,b according to the basic Gould–Jacob reaction.[3] Alkylation of the latter compounds was achieved using different alkylating agents in DMF to allow S_N2 reaction to take place and afford the alkylated ester derivatives of the 4-quinolone **10a–d** and **11a,b**. Alkylation of **9a** resulted in the dialkyl derivative since both N- and O- were alkylated and this was confirmed using ^{1}H NMR and mass spectrometry.

The base hydrolysis of compounds **10a–d** and **11a,b** to give the target compounds **3a,b** and **4a,b** was carried out in THF rather than water to overcome the poor solubility of these compounds in water and to avoid the ease of decarboxylation of β-keto acids upon boiling with aqueous sodium hydroxide.[15] Diazotisation of compound **1** followed by coupling of the diazonium salt with either diethyl malonate or malononitrile in basic medium gave compounds **12** and **13** respectively. The basic medium of this reaction was achieved by using one equivalent of sodium acetate to convert either diethyl malonate or malononitrile into the mono-sodio derivative as a result of removal of one α-proton to yield an ambident anion.[16] This conjugated base will be stabilised by resonance and will react with the diazonium salt to yield compounds **12** and **13**.

Once again the IR spectrum of compound **12** showed two values of the two carbonyl of the two ester groups and this can be attributed to the formation of intra molecular hydrogen bond.

Several attempts were made to prepare 4-oxo-1,4-dihydrocinnoline-3-carboxylic acid using compound **12** but all trials were unsuccessful.

Heating compound **12** with diphenyl ether for 1 hour (*c.f.* quinolone synthesis) resulted in a compound which

Table 1 Anti-infective activity

Compound	*Ps. aeruginosa*	*St. aureus*	*E. coli*	*B. subtilis*
3a	<100	>400	<400	<400
3b	<200	<200	<400	<400
4a	<25	<25	>400	<25
4b	<25	<25	>400	>25
5	<400	<200	>400	>400
Ciproflexacin	< 12.50	< 12.50	< 12.50	<12.50

spectral data indicated is neither compound **12** nor ethyl 4-oxo-1,4-dihydrocinnoline-3-carboxylate.

According to both physical constant (m.p. 322–324 °C) and spectral data, it was found that the given compound was 2-[4-(benzothiazol-2-yl)phenylhydrazono) acetic acid.[12-14] The IR spectrum showed band s at 3325–3266 (NH) cm^{-1}, 1690 (CO) cm^{-1} and the disappearance of band s at 1657 (CO) cm^{-1} and 2983–2930 (CH) aliphatic cm^{-1} which indicated the hydrolysis and decarboxylation of one of the carboxylic groups. The mass spectrum of the unexpected compound is *m/z* 297(13.19%).

Another trial took place when heating compound **12** with either PPA for 3 hours or with $AlCl_3$/chlorobenzene for 6 hours (tracing both reactions with TLC) afforded a compound which was not compound **12** or cinnolone derivative. Upon examining the spectral data besides its melting point it was found that the resulting compound was *N*-4-(benzothiazol-2-yl)phenyl-*N'*-methylene hydrazine.[16-17] IR spectrum revealed the disappearance of band s at 2983–2930 cm^{-1} and band s at 1690 and 1657 cm^{-1} and this indicated that surprisingly hydrolysis and decarboxylation of both carboxylic groups occured. This may be due to the more drustic conditions of both reactions and this was confirmed by ^{1}H NMR (DMSO-d6): δ 4.16 (s, 1H, *H*N–N=C, D_2O exchangeable), 6.95 (s, 2H, N=CH_2) and 7.34–8.05 (m, 8H, ArH) ppm.

From the previously mentioned attempts it was concluded that hydrolysis and decarboxylation of either one or the two carboxylic moieties (according to the reaction time) is faster than intra molecular cyclisation. Cyclisation of compound **13** adopting Friedel–Crafts intra molecular acylation method using $AlCl_3$/chlorobenzene[16-17] resulted in 4-amino-3-cyanocinnoline **5**.

Conclusions

Since quinolone anti-infective agents have broad spectrum activity, the tested compounds were evaluated against different microorganisms including gram-positive microbes (*Staphylococcus aureus* and *Bacillus subtilis*) and gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) using the agar-dilution method according to the National Committee for Clinical Laboratory Standards (NCCLS). The results were expressed as MIC using ciprofloxacin as reference stand ard. Compounds **4a** and **4b** show strong and moderate antibacterial activity while **3a** and **3b**, showed a moderate activity since they lack the C-6 high electronegative atom that can form hydrogen bonding and there is no substituent at C-7 and compound **5** revealed weak activity since it only has about 30% of the criteria that should be present in any structure to show the perfect quinolone antibiotics-like anti-infective activity (Table 1).

Experimental

Melting points were determined in capillary tubes using Griffin apparatus and are uncorrected. Chemical analyses were carried out at the Microanalytical Centre, Cairo University, Giza, Egypt. Infrared spectra were measured on a Schimadzu IR 435 spectrometer. Proton magnetic resonances (^{1}H NMR) were measured at 300 MHz on Varian Gemini spectrophotomer using tetramethylsilane as internal standard (chemical shifts are reported in δ ppm). Mass spectra were obtained on Hewlett Packard 5988 spectrometer.

The following compounds were prepared according to the same reported procedure: 4-benzothiazol-2-yl-phenylamine(**1**)[18] and amino-2-(benzothiazol-2-yl)phenol (**2**).[19]

Ethyl 3-[(4-Benzothiazol-2-yl)phenylamino]-2-cyanoacrylate (**6a**); *Diethyl 2-[(4-benzothiazol-2-yl)phenylamino]methylene] malonate* (**6b**); *ethyl 3-[(3-Benzothiazol-2-yl)-4-hydroxyphenylamino]-2-cyano-acrylate* (**7a**) *and diethyl 2-[-(4-Benzothiazol-2-yl)-4-hydroxyphenyl-amino]methylene]malonate* (**7b**).

Equimolar amounts of either compound **1** or **2** (0.02 mol) with either ethyl 2-cyano-3-ethoxyacrylate or diethyl ethoxymethylenemalonate (0.02 mol) in ethanol (60 ml) was refluxed for 4 h, the reaction mixture was evaporated under reduced pressure and the separated solid was crystallised from ethanol.

6a (A =CN): Yield 80%; m.p. 174–178 °C; IR (KBr): 3421 (NH), 2981–2930 (CH aliphatic) and 2212 (CN) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.26(t, 3H, CH_2CH_3), 4.21 (q, 2H,CH_2CH_3), 7.42–8.13 (m, 8H, ArH), 8.42, 8.62 (2 s, 0.5H, CH=C) and 10.85, 11.00 (2 s, 0.5 *H*, HN, D_2O exchangeable) ppm; EIMS: *m/z* 349 (M^+) (100%); Anal.Calcd for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found; C, 65.80; H, 4.02; N, 12.03%.

6b (A =$COOC_2H_5$): Yield 75%; m.p. 135–137 °C; IR (KBr): 3421 (NH), 2981–2930 (CH aliphatic) and 1676–1671 (C=O) cm^{-1}; ^{1}H NMR (300 MHz,DMSO-d6): δ 1.26(m, 6H, $2CH_2CH_3$), 4.22 (m, 4H, $2CH_2CH_3$), 7.42–8.13 (m, 8H, ArH), 8.48 (d, 1H, CH=C) and 10.87 (d, 1 H, HN, D_2O exchangeable) ppm; Anal.Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07. Found: C, 63.38; H, 4.86; N, 7.23%.

7a (A =CN): Yield 60%; m.p. 199–204 °C; IR (KBr): 3446–3271 (NH and OH), 2984–2927 (CH aliphatic), 2210 (CN) and 1671 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 124 (t, 3H, CH_2CH_3), 4.19 (q, 2H, CH_2CH_3), 7.06–8.29 (m, 7H, ArH), 8.38, 8.42 (2 s, 0.5H, CH=C), 10.75, 10.80 (2 s, 0.5 H, *H*N, D_2O exchangeable) and 11.00 (s, 1 H, OH, D_2O exchangeable) ppm; EIMS: *m/z* 365 (M^+) (100%); Anal.Calcd for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found; C, 62.40; H, 4.40; N, 11.35%.

7b (A =$COOC_2H_5$): Yield 80%; m.p. 154–156 °C; IR (KBr): 3446–3271 (NH and OH),2981–2930 (CH aliphatic), 1705 (C=O) and 1648 (C=O) cm^{-1}; ^{1}H NMR(300 MHz, DMSO-d6): d 1.26(t, 6H, 2 CH_2CH_3), 4.19 (q, 4H, $2CH_2CH_3$), 7.10–8.16 (m, 7H, ArH), 8.34–8.39 (d, 1H, CH=C), 10.74 (d, 1 H, HN, D_2O exchangeable) and (100%); Anal.Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79.Found; C, 61.06; H, 4.73; N, 6.70%.

6-(Benzothiazol-2-yl)-4-oxo-1,4-dihydroquinoline-3-carbo-nitrile(**8a**); *ethyl 6-(benzothiazol-2-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylate* (**8b**); *7-(Benzothiazol-2-yl)-4-oxo-1,4-dihydro-6-hydroxy-quinoline-3-carbonitrile* (**9a**) *and Ethyl 7-(Benzothiazol-2-yl)-4-oxo-1,4-dihydro-6-hydroxyquinoline-3-carboxylate* (**9b**)

A solution of compound **6a, 6b, 7a** or **7b,** (0.01 mol) in diphenyl ether (30 ml) was refluxed for 1 h, cooled, diluted with ether (100 ml) then filtered. The formed precipitate was washed with pet ether (40–60), dried and crystallised from DMF.

8a (A =CN): Yield 70%; m.p. >300 °C; IR (KBr): 3446 (NH) and 2216 (CN) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 7.46–8.74 (m, 7H, ArH), 8.80(s, 1H, CH=C) and 13.00 (s, 1 H, HN,exchangeable) ppm; EIMS: *m/z* 303 (M^+) (100%); Anal.Calcd for $C_{17}H_9N_3OS$:C, 67.31; H, 2.99; N, 13.85. Found; C, 67.06; H, 3.50; N, 13.62%.

8b (A =$COOC_2H_5$): Yield 75%; m.p. >300 °C; IR (KBr): 3421 (NH), and 1631 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 129 (t, 3H, CH_2CH_3), 4.24 (q, 2H, CH_2CH_3), 7.46–8.74 (m, 7H, ArH), 8.80(s, 1H, CH=C) and 12.60 (s, 1 H, HN, D_2O exchangeable) ppm; Anal.Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.11; H, 3.80; N, 7.85%.

9a (A =CN): Yield 60%; m.p. >300 °C; IR (KBr): 3446–3231 (NH and OH), 2211(CN), and 1671 (C=O)cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 6.92–8.72 (m, 6H, ArH), 8.78 (s, 1H, CH=C) and 12.00–12.10 (br s, 2 H, HN and OH, D_2O exchangeable) ppm; EIMS: *m/z* 319 (M^+) (19.8%); Anal.Calcd forr $C_{17}H_9N_3O_2S$: C, 63.94; H, 2.84; N, 13.16.Found; C, 63.80; H, 2.80; N, 12.94%.

9b (A =$COOC_2H_5$): Yield 65%; m.p. >300 °C; IR (KBr): 3446–3231 (NH and OH), 2211(CN), 1703 (C=O) and 1652 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.27 (t, 3H, CH_2CH_3), 4.20 (q, 2H, CH_2CH_3), 6.98–8.66 (m, 6H, ArH), 8.78 (s, 1H, CH=C) and 11.55–11.65 (s, 2 H, HN and OH, D_2O exchangeable) ppm; EIMS: *m/z* 366 (M^+) (33%); Anal.Calcd for $C_{19}H_{14}N_2O_4S$: C, 62.29; H, 3.85; N, 7.65.Found; C,62.30; H,3.70; N, 7.68%.

6-(Benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile (**10a,b**); *Ethyl 6-(Benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylate* (**10c,d**) *and ethyl 7-(benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydro-6-alkoxyquinoline-3-carboxylate* (**11a,b**).

A mixture of compound **8a, 8b** or **9b** (0.01 mol), anhydrous potassium carbonate (0.025 mol) and the appropriate alkyl halide (0.05 mol) in DMF (50 ml) was heated at 80–90 °C for 18–36 h. The reaction mixture was evaporated to dryness and the residue was extracted with ethyl acetate (50 ml). The organic layer was dried (Na_2SO_4), evaporated to dryness then the residue was crystallised from DMF.

10a–d: IR (KBr): 2966–2877 (CH aliphatic), 2222–2207 (CN), 1717–1709 (C=O) and 1631–1627 (C=O) cm^{-1}.

10a (R =CH_3,A=CN): Yield 45%; m.p.> 300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 3.90 (s, 3H, CH_3), 7.46–8.74 (m, 7H, ArH) and 8.81 (s, 1H, CH=C) ppm; EIMS: *m/z* 317(M^+) (100%); Anal.Calcd for $C_{18}H_{11}N_3OS$: C, 68.12; H, 3.49; N, 13.24.Found; C, 68.04; H,3.56; N,13.20%.

10b (R=C_2H_5,A=CN): Yield 50%; m.p.> 300 °C; EIMS: *m/z* 331(M^+) (100%); Anal.Calcd for $C_{19}H_{13}N_3OS$: C, 68.86; H, 3.95; N, 12.68. Found: C, 68.70; H, 4.00; N, 12.72%.

10c (R =CH_3, A =$COOC_2H_5$): Yield 47%; m.p. > 300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.29 (t, 3H, CH_2CH_3), 3.90 (s, 3H, CH_3), 4.23 (q, 2H, CH_2CH_3), 7.48–8.78 (m, 7H, ArH) and 8.84 (s, 1H, CH=C) ppm; EIMS: *m/z* 364 (M^+) (1.6%); Anal.Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.92; H,4.43; N, 7.69. Found: C, 65.80; H, 4.50; N,7.67%.

10d (R =C_2H_5, A =$COOC_2H_5$): Yield 43%; m.p. > 300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.1871.36 (m, 6H, $2CH_2CH_3$), 4.18–4.46 (m, 4H, $2CH_2CH_3$), 7.00–8.71 (m, 7H, ArH) and 8.83 (s, 1H, CH=C) ppm; Anal.Calcd for $C_{21}H_{18}N_2O_3S$:C, 66.65; H,4.79; N, 7.40. Found: C, 66.52; H,4.64; N, 7.85%.

11a, b: IR (KBr): 2966–2877 (CH aliphatic), 1704 (C=O) and 1610 (C=O) cm^{-1}.

11a (R =CH_3,A =$COOC_2H_5$): Yield 50%; m.p. > 300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.19 (t, 3H, CH_2CH_3), 3.82–4.15 (m, 8H, CH_2CH_3, NCH_3 and OCH_3) 7.05–8.21 (m, 6H, ArH) and 8.56 (s, 1H, CH=C) ppm; Anal.Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10. Found: C, 63.70; H, 4.41; N, 7.15%.

11b (R =C_2H_5,A =$COOC_2H_5$):Yield 50%; m.p.> 300 °C; ^{1}H NMR (300 MHz, DMSO-d6):d 1.05–1.54 (m, 9H, CH_2CH_3), 4.42–4.46 (m, 6H, CH_2CH_3), 6.99–8.11 (m, 6H, ArH) and 8.17 (s, 1H, CH=C) ppm; EIMS: *m/z* 422 (M^+) (38.7%), Anal.Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.26; H, 5.28; N, 7.10%.

Diethyl2-[4-(benzothiazol-2-yl)phenyl hydrazono]malonate **(12)**, *2-[(4-Benzothiazol-2yl)phenylhydrazono]malononitrile* **(13)**

To an ice-cold solution of **1** (0.01 mol) in hydrochloric acid (2.5 ml) and distilled water (5 ml), a solution of sodium nitrite (0.013 mol) in distilled water (5 ml) was added portionwise. This solution was added portionwise to a well-stirred cooled solution of either diethyl malonate (0.01 mol) or malononitrile (0.01 mol) in aqueous ethanol (10 ml, 50%) containing sodium acetate (0.011 mol). After completion of addition, the reaction mixture was kept in ice for 2 h and then filtered. The product was dried and then crystallised from the appropriate solvent(s).

12: Yield 75% (ethanol); m.p. 93–95 °C; IR (KBr): 3400–3100 (NH), 2950 (CH aliphatic), 1699 (C=O), 1657(C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): 1.32 (t, 6H, $2CH_3$), 4.35(q, 4H, $2CH_2$), 7.52–8.13 (m, 8H, ArH) and 11.97(s, 1H, *H*N–N=C, D_2O exchangeable) ppm; EIMS: *m/z* 397(M + .) (62.74%). Anal.Calcd for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.63; H 5.01; N, 10.27%.

13:Yield 85% (DMF/MeOH); m.p. 299–300 °C; IR (KBr): 3500–3200 (NH), 2200 (CN) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 3.32 (s, 1 H, *H*N–N=C, D_2O exchangeable) and 7.4–8.1 (m, 8H, ArH) ppm; EIMS: *m/z* 303 (M^+) (100%). Anal.Calcd for $C_{16}H_9N_5S$: C, 63.35; H, 2.99; N, 23.09. Found: C, 63.60; H, 3.00; N, 23.09%.

6-(Benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylicacid **(3a,b)**; *7-(Benzothiazol-2-yl)-1-alkyl-4-oxo-1,4-dihydro-6-alkoxyquinoline-3-carboxylic acid* **(4a,b).**

A mixture of compound **10a, 10b, 10c, 10d, 11a** or **11b** (0.01 mol) and sodium hydroxide (2N, 10.5 ml) in tetrahydrofuran (60 ml) was heated under reflux for 24 h. THF was evaporated to dryness, water was added to the residue and the mixture was filtered. The filtrate was acidified with hydrochloric acid (6N) and then the formed precipitate was filtered, dried and crystallised from DMF.

3a,b: IR (KBr): 3500–3000 (OH), 2974 (CH aliphatic), 1717–1715 (C=O) and 1631–1627 (C=O) cm^{-1}.

3a (R = CH_3): Yield 50%; m.p. >300 °C; EIMS: *m/z* 336 (M^+) (11.3%); Anal.Calcd for $C_{18}H_{12}N_2O_3S$: C, 64.27; H, 3.60; N, 8.33. Found: C, 63.90; H, 3.67; N, 8.27%.

3b (R = C_2H_5): Yield 50%; m.p. >300 °C; ^{1}H NMR (300 MHz, DMSO-d6): d 1.44–1.48 (t, 3H, NCH_2CH_3), 4.59–4.68 (q, 2H, NCH_2CH_3), 7.47–8.95 (m, 7H, ArH), 8.91 (s, 1H, CH=C) and 14.85 (s, 1 H, OH, D_2O exchangeable) ppm; EIMS: *m/z* 350 (M^+) (12.3%); Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.52; H, 3.96; N, 7.76%.

4a,b: IR (KBr): 3500–3000 (OH), 2961 (CH aliphatic), 1672, 1652 (C=O) and 1621, 1611 (C=O) cm^{-1}.

4a (R =CH_3): Yield 70%; m.p. >300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 4.39 (s, 6H, NCH_3 and O CH_3), 7.45–8.84 (m, 6H, ArH), 8.92 (s, 1H, CH=C) and 12.00 (s, 1 H, O*H*, D_2O exchangeable) ppm; EIMS: *m/z* 366 (M^+) (18%); Anal.Calcd for $C_{19}H_{14}N_2O_4S$: C, 62.28; H, 3.85; N, 7.65. Found: C, 62.50; H, 3.56; N, 7.67%.

4b (R = C_2H_5): Yield 50%; m.p. >300 °C; ^{1}H NMR (300 MHz, DMSO-d6): δ 1.52 (t, 3H, NCH_2CH_3), 1.59(t, 3H, OCH_2CH_3), 4.42–4.46 (q, 2H, NCH_2CH_3), 4.65 (q, 2H, OCH_2CH_3), 7.49–8.15 (m, 5H, ArH), 8.87(s, 1H, Ar H, 9.02 (s, 1H, CH=C) and 15.09 (s, 1 H, O*H*, D_2O exchangeable) ppm; EIMS: *m/z* 395 (M^+ + 1) (28%); Anal.Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10. Found: C, 64.12; H, 4.54; N, 7.14%

4-Amino-6-(benzothiazol-2-yl)cinnoline-3-carbonitrlie **(5):** A mixture of compound **12** (0.01 mol), anhydrous aluminum chloride (0.04 mol) and chlorobenzene (30 ml) was refluxed for 6 h, hydrochloric acid (2N,20 ml) was then added portionwise under ice cooling to the reaction mixture which was then heated at 90 °C for 10 min, cooled and set aside. The separated solid was filtered, washed with absolute ethanol. The salt was neutralised with saturated solution of sodium carbonate. The solid product was collected and crystallised from DMF to give 1.51 gm of **5** (50%); m.p. 253–255 °C; IR (KBr): 3382–3219 (NH_2), 2223 (CN) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ 5.86 (s, 2H, NH_2, D_2O exchangeable) and 6.64–8.12 (m, 7H, ArH) ppm; Anal.Calcd for $C_{16}H_9N_5S$: C, 63.35; H, 2.99; N, 23.09. Found: C, 63.92; H, 3.11; N, 23.09%.

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