Synthesis of (*Z*)-2-(4-(arylimino)-3,4-dihydroquinazolin-2(1*H*)-ylidene)-1*H*-indene-1,3(2*H*)dione using 2-amino-*N'*-aryl-benzimidamides as a starting material

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The reaction between 2-amino-*N'*-arylbenzimidamide derivatives (**3a–g**) and 2-dicyanomethyleneindan-1,3-dione (**4**, CNIND) is described. The product that was obtained in moderate to good yields *via* CT-complexation is identified as (*Z*)-2-[4-(arylimino)-3,4-dihydroquinazolin-2(1*H*)-ylidene]-1*H*-indene-1,3(2*H*)-dione (**5a–g**).

Keywords: electron donor–acceptor, 2-amino-*N'*-arylbenzimidamides, 2-dicyanomethyleneindan-1,3-dione, quinazolines

The chemistry and applications of 2-amino-*N'*-arylbenzimidamides have received much attention due to their usefulness as synthetic intermediates and their biological importance.[1,2] This intermediate was used to synthesise quinazoline derivatives which constitute an important class of heterocyclic compounds and they form a large number of products with a broad spectrum of biological activities.[3–5]

The precursors for our study have been described previously; the yields of the respective amidines were low, and the applied protocol could not be applied to synthesise alkoxy and dihalo derivatives.[6] This prompted us to synthesise different 2-amino-*N'*-aryl-benzimidamide derivatives (**3a–g**) containing a variety of substituents including alkoxy- and dihalo-moieties as substituent groups in good yields by treatment of 2-aminobenzonitrile (**1**) with aniline derivatives **2a–g** in the presence of aluminum chloride as a catalyst (Scheme 1).[6,7]

Organic molecules containing electron donor and acceptor moieties are interesting because of their optical and electronic properties.[8] Recently, we have succeeded in preparing a variety of poorly investigated types of heterocyclic compounds such as quinazoline and diazepine derivatives, *via* CT-complexes by the reaction of 2-amino-*N'*-arylbenzimidamides (**3a–g**) with some selected π-acceptors such as tetracyanoethylene (TCNE),[7] 2,3-dichloro-1,4-naphthoquinone (DCHNQ)[9] and 7,7,8,8-tetracyanoquinodimethane (TCNQ).[10]

Results and discussion

Continuing our work on the synthesis of 2,4-disubstituted quinazoline derivatives, we now describe the reaction of 2-amino-*N'*-arylbenzimidamides (**3a–g**) with CNIND.

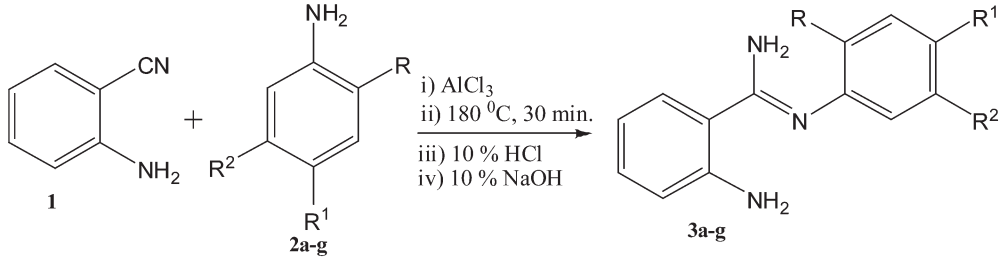
Addition of the electron donor **3a–g** to the electron acceptor **4** in dry ethyl acetate leads to complex formation which has a deep red colour. The colour of the obtained complex gradually disappears to give rise to the formation of a single new reaction product to which structure (*Z*)-2-(4-(arylimino)-3,4-dihydroquinazolin-2(1*H*)-ylidene)-1*H*-indene-1,3(2*H*)-dione was assigned on the basis of the spectroscopic data as well as elemental analysis (Scheme 2). The two $-NH_2$ groups of **3a–g** participated in the reaction, in which two equivalents of HCN were eliminated to give the adducts **5a–g**. This could be rationalised in terms of the stability of the products **5a–g**, due to the intramolecular hydrogen bonds which are further substantiated from the down field shift of the two –NH groups (δ ≈13.2, 10.2 ppm), as well as, the ν_{max} of this group at ≈3300 cm^{-1}.

As a typical example, the IR spectrum of the product **5a** displayed a strong absorption maxima at ν = 3238 cm^{-1} indicating the presence of an NH group, while the CO group absorbs at ν = 1689 cm^{-1}. Furthermore, the IR spectrum reveals no absorption peaks characteristic for the cyano groups. Taking the ^{1}H NMR spectrum of the main product **5a** as an example it exhibits beside the signals due to the aromatic protons in their expected positions two broad signals at δ = 13.25 and 10.27 ppm due to the two NH groups. The ^{13}C NMR spectrum showed the existence of 18 distinct carbon atoms, two of them resonated at δ = 179.41 ppm characteristic for the two carbonyl groups. Another carbon atom resonated at δ = 93.57 ppm for OC–C–CO and another carbon resonated at δ = 99.78 ppm for HN–C–NH carbon atom. However, the C=N resonated at δ = 156.83 ppm. Both MS and elemental analysis confirm the molecular formula of **5a** as $C_{23}H_{15}N_3O_2$.

The ^{1}H and ^{13}C NMR spectra of the products **5b–g** were similar to those of **5a** except for the second aryl group, which exhibited characteristic signals with appropriate chemical shifts. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values (see Experimental section).

The formation of the products **5a–g** can be rationalised according to the pathway shown in Scheme 3.

With regard to the reaction mechanism, we propose that the reaction begins with a nucleophilic attack of the aromatic amino group of **3a–g** to the reactive carbon atom that carries two cyano groups {$C(CN)_2$} of **4**, this is followed by losing a molecule of HCN to give the intermediate **6a–g**. This intermediate can subsequently be cyclised by nucleophilic attack of the aliphatic amino group to the same carbon atom, this follows by eliminating another molecule of HCN to form the products **5a–g**.



Scheme 1 Synthesis of 2-amino-*N'*-arylbenzimidamides (**3a–g**).

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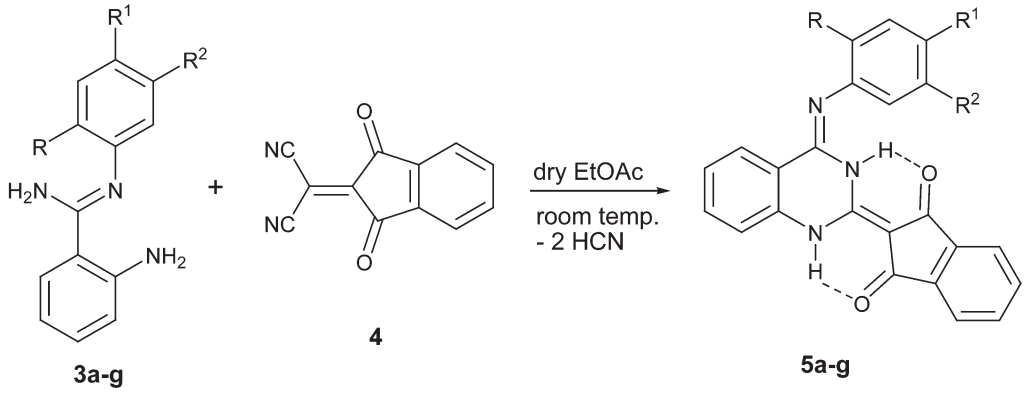


3a-g 4 5a-g

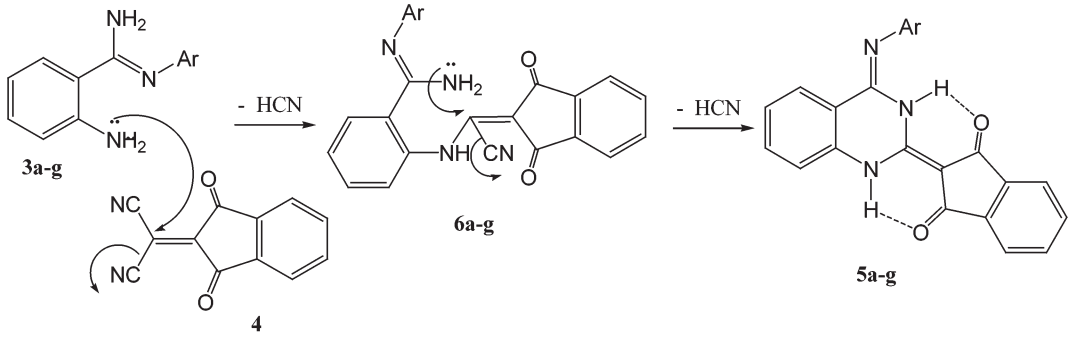
3,5

a, R = R^1 = R^2 = H **b**, R = R^2 = H, R^1 = Cl **c**, R = R^1 = H, R^2 = Cl

d, R^1 = R^2 = H, R = Cl **e**, R = R^1 = H, R^2 = Br **f**, R = R^2 = H, R^1 = Br

g, R^1 = R^2 = H, R = Et

Scheme 2 Reaction of 2-amino-*N′*-arylbenzimidamides (**3a–g**) with CNIND (**4**).



3a-g 6a-g 5a-g 4

Scheme 3 Rational pathway for the formation of compounds **5a–g**.

Conclusion

Synthesis of (*Z*)-2-(4-(arylimino)-3,4-dihydroquinazolin-2(1*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-diones by CT-complexation is successful and the products are obtained in good yields. The simplified workup procedure, in addition to the mild and neutral reaction conditions, are the main advantages of this approach.

Experimental

All reagents were purchased from Alfa Aesar and Fluka companies and were used without further purification. 2-amino-*N′*-arylbenzimidamides (**3a–g**) were prepared according to established methods.[6,7] Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by TLC, on aluminum plates coated with silica gel with fluorescent indicator (Merck, 60 F_{254}) using $CHCl_3$:CH_3COCH_3 (7:3) as eluent. The IR spectra were recorded on a Jasco FT′IR-450 Plus IR spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR), with deuterated chloroform ($CDCl_3$) and DMSO-d_6, as solvents. Chemical shifts are quoted in δ and are referenced to TMS. The mass spectra were recorded on a Trace GC 2000 / Finnegan Mat SSQ 7000 and a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were measured with a Vario EL III CHNOS.

*Reactions of 2-amino-N′-arylbenzimidamides (***3a–g***) with 2-dicyanomethyleneindan-1,3-dione (CNIND,* **4***); general procedure*

To a well-stirred solution of (0.55 mmol) 2-dicyanomethyleneindan-1,3-dione (CNIND, **4**) dissolved in dry ethyl acetate (15 mL) a solution of (0.5 mmol) of 2-amino-*N′*-arylbenzimidamides (**3a–g**) dissolved in dry ethyl acetate (15 mL) was added dropwise with constant stirring. The colour of the reaction mixture changed from yellow to deep red followed by formation of a precipitate. The reaction mixture was stirred at room temperature for a further 2–3 h and was followed by TLC. After consumption of the reactants the formed precipitate was collected by filtration, washed and recrystallised from ethyl acetate to afford products **5a–g** in 48–76% yield.

(Z)-2-Amino-N′-(2-ethylphenyl)benzimidamide **(3g):** Pale yellow solid; yield: 1.07 g, 48%; m.p. 147–148 °C; ^{1}H NMR (300 MHz, d_6-DMSO): 7.55–7.48 (m, 1 H), 7.17–7.11 (m, 3 H), 6.82 (s, 2 H, NH_2), 6.79–6.75 (m, 2 H), 6.67–6.62 (m, 2 H), 5.94 (s, 2 H, NH_2), 2.72 (q, 2 H, *J* = 4.35 Hz), 1.21 (t, 3 H, *J* = 6.99 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 156.38, 149.97, 146.05, 132.51, 130.12 (CH), 128.49 (CH), 127.16 (CH), 123.92 (CH), 120.08 (CH), 120.07 (CH), 118.14 (CH), 117.10 (CH), 24.52 (CH_2), 15.13 (CH_3) ppm; IR (KBr): ν_{max} = 3238, 3047, 1689, 1631, 1587 cm^{-1}; MS (EI): *m/z*(%) = 239 (M^+, 71), 224 (M^+ - CH_3, 46), 210 (M^+ - Et, 42), 183 (10), 176 (9), 149 (34), 130 (28), 119 (11), 106 (100), 97 (26), 91 (24), 77 (49), 57 (39). Anal. Calcd for $C_{15}H_{17}N_3$ (239.32): C, 75.28; H, 7.16; N, 17.56. Found: C, 75.10; H, 7.11; N, 17.39%.

(Z)-2-(4-(Phenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5a):** Yellow solid; yield: 136 mg, 70%; m.p. 308–309 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.25 (s, 1 H, NH), 10.27 (s, 1 H, NH), 8.60 (d, 1 H, *J* = 8.36 Hz), 8.07–7.93 (m, 3 H), 7.88–7.60 (m, 4 H), 7.76–7.67 (m, 2 H), 7.36–7.29 (m, 3 H) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.41, 156.83, 153.53, 139.01, 138.49, 138.13, 135.01 (2CH), 132.40 (2CH), 128.49 (CH), 124.94 (CH), 124.56 (CH), 123.92 (CH), 122.08 (2CH), 120.07 (CH), 118.14 (CH), 111.88 (CH), 99.78 (OC–C–CO), 93.57 (HN–C–NH) ppm; IR

(KBr): ν_{max} = 3238, 3047, 1689, 1631, 1587 cm^{-1}; MS (EI): MS (EI): *m/z*(%) = 365 (M^+, 100), 364 (M^+ - 1, 65), 347 (M^+ - H_2O, 5), 323 (2), 307 (4), 282 (2), 260 (6), 222 (2), 205 (2), 154 (3), 104 (8), 89 (10), 77 (42), 76 (18), 62 (7). Anal. Calcd for $C_{23}H_{15}N_3O_2$ (365.38): C, 75.60; H, 4.14; N, 11.50. Found: C, 75.46; H, 4.12; N, 11.35%.

(Z)-2-(4-(4-Chlorophenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5b):** Pale yellow solid; yield: 145 mg, 69%; m.p. 321–323 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.21 (s, 1 H, NH), 10.38 (s, 1 H, NH), 8.57 (d, 2 H, *J* = 7.99 Hz), 8.46–8.41 (m, 2 H), 7.37 (t, 1 H, *J* = 7.65 Hz), 7.32 (t, 1 H, *J* = 7.05 Hz), 7.27–7.23 (m, 4 H), 7.20 (d, 2 H, *J* = 7.92 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.94, 158.19, 152.03, 139.18, 138.01, 137.54, 135.09 (2CH), 131.14, 128.41 (CH), 124.98 (CH), 124.56 (CH), 123.92 (CH), 122.16 (2CH), 119.79 (CH), 117.94 (CH), 112.06 (CH) 100.31 (OC–C–CO), 91.97 (HN–C–NH) ppm; IR (KBr): ν_{max} = 3330, 3202, 1625, 1586 cm^{-1}; MS (EI): *m/z*(%) = 401 (M^{+2}, 58), 400 (M^{+1}, 43), 399 (M^+, 77), 398 (M^+ –1, 10), 372 (35), 354 (34), 339 (20), 277 (34), 254 (100), 243 (38), 228 (25), 219 (38), 205 (37), 193 (29), 177 (36), 159 (30), 118 (34), 111 (82), 85 (35), 53 (25). Anal. Calcd for $C_{23}H_{14}ClN_3O_2$ (399.83): C, 69.09; H, 3.53; Cl, 8.87; N, 10.51. Found: C, 68.86; H, 3.47; Cl, 8.67; N, 10.38%.

(Z)-2-(4-(3-Chlorophenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5c):** Yellow solid; yield: 132 mg, 63%; m.p. 326–328 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.27 (s, 1 H, NH), 10.13 (s, 1 H, NH), 8.18–8.14 (m, 2 H), 8.03–7.98 (dd, 1 H, *J* = 1.81, 1.73 Hz), 7.76–7.72 (m, 1 H), 7.49–7.44 (m, 3 H), 7.37–7.31 (m, 4 H), 7.27 (t, 1 H, *J* = 1.02) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.97, 158.39, 153.83, 139.19, 138.11, 137.34, 135.09 (2CH), 133.34 (C–Cl), 127.41 (CH), 124.98 (CH), 123.96 (CH), 122.84 (CH), 121.03 (2CH), 119.79 (CH), 117.94 (CH), 113.66 (CH) 101.01 (OC–C–CO), 94.77 (HN–C–NH) ppm; IR (KBr): ν_{max} = 3349, 3270, 3065, 1638, 1584 cm^{-1}; MS (EI): *m/z*(%) = 401 (M^{+2}, 22), 400 (M^{+1}, 28), 399 (M^+, 32), 398 (M^+ –1, 23), 390 (10), 372 (8), 364 ((M^+- Cl, 9), 282 (7), 269 (98), 225 (33), 253 (100), 244 (9), 220 (15), 187 (11), 172 (22), 154 (11), 129 (17), 114 (16), 111 (23), 89 (18), 76 (27), 63 (16). Anal. Calcd for $C_{23}H_{14}ClN_3O_2$ (399.83): C, 69.09; H, 3.53; Cl, 8.87; N, 10.51. Found: C, 68.85; H, 3.50; Cl, 8.72; N, 10.37%.

(Z)-2-(4-(2-Chlorophenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5d):** Yellow solid; yield: 101 mg, 48%; m.p. 332–334 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.24 (s, 1 H, NH), 10.27 (s, 1 H, NH), 7.96–7.92 (m, 2 H), 7.77–7.73 (m, 2 H), 7.53–7.47 (m, 4 H), 7.34–7.29 (m, 2 H), 7.13–7.10 (m, 2 H) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.01, 158.39, 144.03, 139.59, 139.01, 135.01 (2CH), 130.1 (CH),130.95 (CH), 128.41 (CH), 127.74 (C-Cl), 126.81 (CH), 123.96 (CH), 118.79(CH), 118.52 (CH), 114.13 (CH) 100.81 (OC–C–CO), 93.79 (HN–C–NH) ppm; IR (KBr): ν_{max} = 3238, 3047, 1689, 1631, 1587 cm^{-1}; MS (EI): *m/z*(%) = 401 (M^{+2}, 26), 400 (M^{+1}, 39), 399 (M^+, 39), 398 (M^+–1, 100), 390 (6), 375 (5), 363 ((M^+- Cl, 41), 346 (10), 311 (8), 285 (2), 270 (25), 227 (15), 220 (11), 100 (6), 95 (11), 76 (4). Anal. Calcd for $C_{23}H_{14}ClN_3O_2$ (399.83): C, 69.09; H, 3.53; Cl, 8.87; N, 10.51. Found: C, 68.88; H, 3.49; Cl, 8.68; N, 10.35%.

(Z)-2-(4-(3-Bromophenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5e):** Yellowish brown solid; yield: 176 mg, 76%; m.p. 300–302 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.27 (s, 1 H, NH), 10.23 (s, 1 H, NH), 8.26 (dd, 1 H, *J* = 1.68, 1.71 Hz), 8.19–8.15 (m, 3 H), 7.90–7.86 (m, 2 H), 7.79–7.74 (m, 2 H), 7.68–7.61 (m, 4 H) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.23, 159.06, 154.91, 139.59, 138.89, 135.12 (2CH), 130.11 (CH), 126.81 (CH), 125.05 (CH), 124.10 (CH), 123.13 (CH), 123.96, 121.32 (CH), 118.82 (CH), 112.98 (CH) 102.31 (OC–C–CO), 92.80 (HN–C–NH) ppm; IR (KBr): ν_{max} = 3348, 3267, 3060, 1634, 1631, 1583 cm^{-1}; MS (EI): *m/z*(%) = 446 (M^{+2}, 41), 444 (M^+, 39), 443 (M^+ -1, 76), 417 (24), 400 (11), 372 (14), 364 (M^+- Br, 15), 347 (29), 329 (11), 300 (22), 273 (21), 266 (15), 259 (30), 219 (31), 197 (14), 182 (44), 148 (14), 114 (29), 103 (20), 89 (47), 75 (26), 65 (30). Anal. Calcd for $C_{23}H_{14}BrN_3O_2$ (444.28): C, 62.18; H, 3.18; N, 9.46. Found: C, 61.97; H, 3.12; N, 9.29%.

(Z)-2-(4-(4-Bromophenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5f):** Brown solid; yield: 139 mg, 60%; m.p. 312–314 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.28 (s, 1 H, NH), 10.26 (s, 1 H, NH), 8.68 (d, 2 H, *J* = 7.49 Hz), 8.57–8.50 (m, 2 H), 7.82 (d, 2 H, *J* = 7.51 Hz), 7.72–7.69 (m, 1 H), 7.59–7.55 (m, 4 H), 7.31 (t, 1 H, *J* = 6.90 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.25, 159.11, 151.77, 139.91, 138.87, 135.05 (2CH), 1302.19 (2CH), 126.76 (CH), 124.14 (CH), 122.33 (2CH), 121.32, 118.82 (CH), 113.89 (CH) 99.76 (OC–C–CO), 94.78 (HN–C–NH) ppm; IR (KBr): ν_{max} = 3357, 3133, 3038, 1669, 1641, 1587 cm^{-1}; MS (EI): *m/z*(%) = 446 (M^{+2}, 37), 444 (M^+, 43), 443 (M^+–1, 100), 440 (11), 376 (12), 372 (14), 367 (14), 364 (M^+ - Br, 17) , 337 (13), 314 (11), 276 (10), 260 (19), 258 (87), 230 (18), 190 (28), 164 (18), 156 (14), 144 (11), 101 (12), 86 (25), 75 (26), 64 (10). Anal. Calcd for $C_{23}H_{14}BrN_3O_2$ (444.28): C, 62.18; H, 3.18; N, 9.46. Found: C, 62.03; H, 3.16; N, 9.34%.

(Z)-2-(4-(2-Ethylphenylimino)-3,4-dihydroquinazolin-2(1H)-ylidene)-1H-indene-1,3(2H)-dione **(5g):** Yellow solid; yield: 128 mg, 62%; m.p. 292–294 °C; ^{1}H NMR (300 MHz, d_6-DMSO): δ = 13.15 (s, 1 H, NH), 10.27 (s, 1 H, NH), 8.52–8.47 (m, 2 H), 8.32–8.27 (m, 1 H), 8.23–8.20 (m, 1 H), 7.88–7.84 (m, 3 H), 7.66–7.49 (m, 5 H), 2.51 (q, 2 H, *J* = 2.33 Hz), 1.17 (t, 3 H, *J* = 1.91 Hz) ppm; ^{13}C NMR (75 MHz, d_6-DMSO): δ = 179.09, 157.24, 150.04, 139.49, 137.54, 135.11 (2CH), 133.84, 130.67 (CH), 127.41 (CH), 126.19 (2CH), 124.02 (CH), 120.90 (CH), 120.10 (CH), 118.79 (CH), 114.14 (CH), 102.06 (OC–C–CO), 94.63 (HN–C–NH), 23.48 (CH_2), 15.01 (CH_3) ppm; IR (KBr): ν_{max} = 3294, 3043, 1706, 1611, 1564, cm^{-1}; MS (EI): *m/z*(%) = 394 (M^{+1}, 40), 393 (M^+, 45), 381 (33), 377 (36), 365 (M^+ - Et, 41), 359 (45), 343 (43), 331 (39) 308 (37), 292 (37), 276 (49), 285 (39), 241 (51), 212 (46), 186 (61), 163 (47), 143 (54), 137 (64), 97 (81), 84 (91), 77 (38), 66 (22), 60 (100)). Anal. Calcd for $C_{25}H_{19}N_3O_2$ (393.44): C, 76.32; H, 4.87; N, 10.68. Found: C, 76.17; H, 4.83; N, 10.53%.

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References

1 D.D. Díaz and M.G. Finn, *Chem. Eur. J.*, 2004, **10**, 303.
2 V.G. Granik, *Usp. Khim.*, 1983, **52**, 669.
3 M.F. Brana, J.M. Castellano, G. Keilhauer, A. Machuca, Y. Martina, C. Redondo, E. Schlick and N. Walker, *Anti-Cancer Drug Des.*, 1994, **9**, 527.
4 T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger and M. Stamminger, *Antimicrob.Agents Chemother.*, 2004, **48**, 4154.
5 S. Madapa, Z. Tusi, A. Mishra, K. Srivastava, S.K. Pandey, R. Tripathi, S.K. Puri and S. Batra, *Bioorg. Med. Chem.*, 2009, **17**, 222
6 W. Szczepankiewicz, J. Suwinski and R. Bujok, *Tetrahedron,* 2000, **56**, 9343.
7 K.M. El-Shaieb, H. Hopf and P.G. Jones, *Z. Naturforsch.*, 2009, **64b**, 858.
8 B. Illescas, N. Martin, J.L. Segura and C. Seoane, *J. Org. Chem.*, 1995, **60**, 5643.
9 K.M. El-Shaieb, *J. Chem. Res.*, 2010, 137.
10 F.F. Abdel-latif, K.M. El-Shaieb and A.G. El-Deen, *J. Chem. Res.*, 2010, 449.