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NEW 1,2- AND 1,3-AZA-YLIDES OF 3-AMINO-2-SUBSTITUTED-1*H*-ISOINDOLES

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Abstract – The reaction of 2-(bromomethyl)benzonitrile (**5**) with hydrazides **6a-f** or heterocyclic amines **14a-c** gave isoindolium bromides **7a-f** and **15a-f**, respectively. Deprotonation of the latter salts afforded the 1,2-aza-ylides **8a-f** and 1,3-aza-ylides **16a-c** instead of the analogous imines **9a-f** or **17a-c**, respectively. Single crystal X-ray and NMR analyses confirmed the stable ylide structures of **8a-f** and **16a-c** and established the presence of a complete benzenoid unit in the isoindole moiety, in both the solid state and solution phase.

INTRODUCTION

Isoindoles are particularly useful for treating diseases caused or aggravated by excessive or unregulated levels of tumour necrosis factor alpha (TNF-α), interleukin-beta (IL-β), interleukin-10 (IL-10) or T lymphocytes (T-cells). For example, these compounds are effective for treating cancer, viral, genetic, inflammatory, allergic, autoimmune and bacterial diseases.[1,2] Thalidomide, an isoindole derivative, is an emerging immunotherapeutic agent. In addition to its utility in treating a variety of inflammatory disorders, it is useful for treating cancers and has been shown to inhibit the production of both TNF-α and IL-β while simultaneously increasing the production of IL-10 and T-cells. The teratogenic properties of thalidomide have limited its use and driven efforts to discover new related inhibitors of TNF-α production with improved therapeutic activity and reduced toxicity.[3-6] Despite this research, there remains a need for non-toxic and high-potency compounds that treat or prevent cancer, inflammatory disorders, and

autoimmune diseases. Therefore, the synthesis and chemical reactivity of isoindole derivatives have received considerable interest.[7,8]

The 2*H*-isoindole tautomer (**1**) (Figure 1a) is the predominant form in solution and is associated with lower aromaticity, as its six-membered ring is not a complete benzenoid unit. The alternative 1*H*-isoindole tautomer (**2**) (Figure 1a), which contains a complete benzenoid unit, exists in an appreciable percentage in equilibrium with the 2*H*-isoindole tautomer (**1**). The position of this equilibrium can be altered by changing the solvent. Solvents such as dimethylsulphoxide (DMSO) tend to favour the 2*H*-isoindole tautomer, while protic solvents such as methanol favour the 1*H*-isoindole tautomer.[9-12]

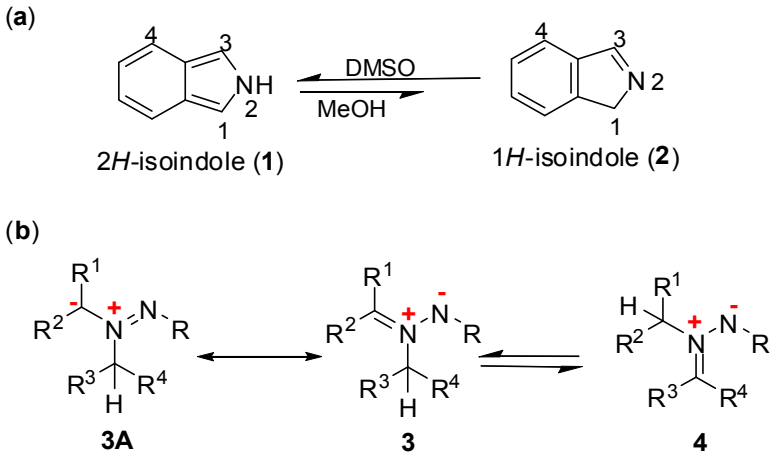


Figure 1. DMSO-MeOH equilibrium of 2*H*-isoindole (**1**) and 1*H*-isoindole (**2**). **Figure 1b**. Resonance and tautomerization of 1,2-aza-ylides **3**

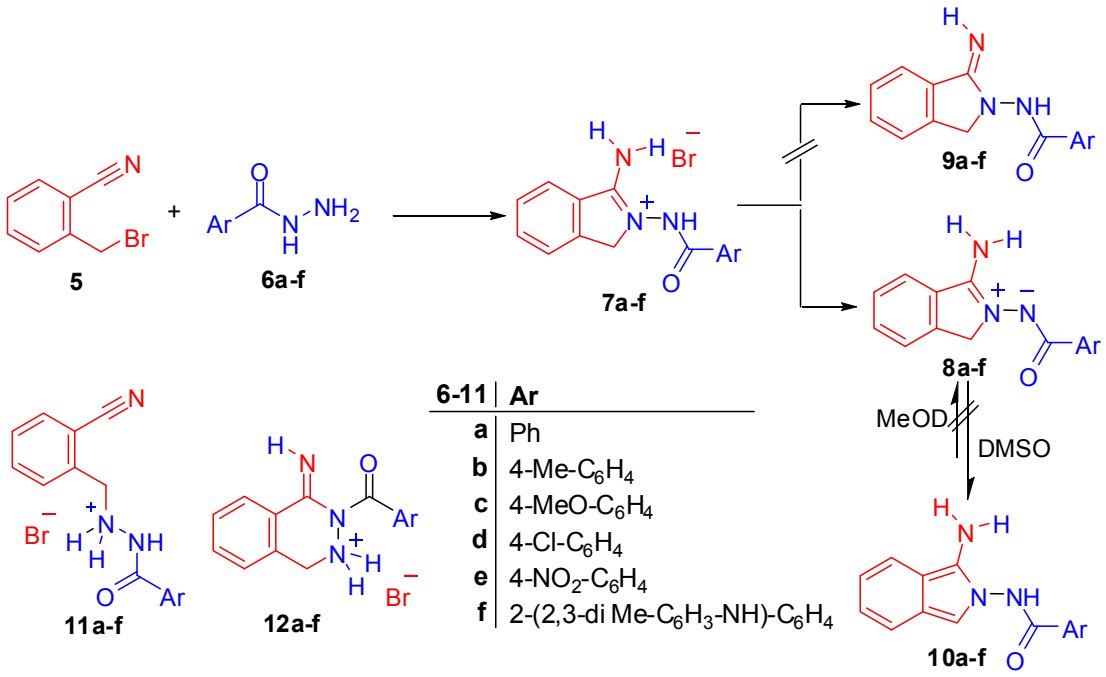
On the other hand, there has been a rapid increase in the use of ylides in organic synthesis. Despite the instability of nitrogen ylides, they are highly reactive intermediates and have a rich chemistry that can be used for the rapid preparation of highly functionalised compounds from relatively simple components. *N*-Ylide chemistry now includes a large area of research and embodies a broad range of synthetic and mechanistic work concerning both the generation and reactions of ylides.[13] 1,2-Aza-ylides, or 1,2-dipole aza compounds, are neutral dipolar molecules containing a negatively charged nitrogen atom directly attached to another nitrogen atom with a positive charge, with both nitrogen atoms having full octets of electrons. When 1,2-dipole aza compounds are attached to a carbon atom, they form 1,3-dipole molecules represented as an allyl structure (-C=N-N-) in which the 1,3-dipole shares four π-system electrons over three atoms, such as in ylides **3** (Figure 1b).[13]

In continuation of our interest in the construction of novel heterocycles of chemical and/or pharmaceutical interest,[14-21] in this work we aimed to study the reaction of 2-(bromomethyl)benzonitrile

(**5**) with hydrazides **6a-f** or heterocyclic amines **14a-c** (Schemes 1 and 2), which produced stable 1,2- and 1,3-aza-ylides of isoindole containing a complete benzenoid unit in the solid state and solution phase.

RESULTS AND DISCUSSION

The reaction of 2-(bromomethyl)benzonitrile (**5**) with the appropriate hydrazides **6a-f** in methanol under microwave irradiation (200 W, 90 °C) for 4 min gave, in each case, a single product in good yield (75-92%). The products were identified as isoindolium bromides **7a-f** (Scheme 1) based on single crystal X-ray analysis of compound **7f**[22] (Figure 2). Salts **7a-f** were also prepared conventionally in refluxing methanol for 10 h in 40-68% yield.



Scheme 1. Synthesis of isoindolium 1,2-aza-ylides **8a-f**

Interestingly, deprotonation of bromides **7a-f** with sodium carbonate at ambient temperature afforded the 1,2-aza-ylides **8a-f** based on single crystal X-ray analysis of compound **8a**[22] (Figure 3), which excluded the possibility of the formation of imines **9a-f** in the solid state. IR spectra of compounds **8a-f** revealed two sharp absorption bands characteristic of a quaternary ammonium cation (≡N^+-) in the region of 2362-2339 cm^{-1}. A carbonyl absorption band also appeared at 1699-1676 cm^{-1} in addition to the NH_2 absorption band at 3405-3047 cm^{-1}. The ^1H NMR (DMSO-d_6) spectra of **8a-f** did not indicate the presence of a pyrrole -CH= proton due to the expected equilibrium with **10a-f**. However, the spectra contained a singlet signal due to -CH_2- protons in the region of δ 5.23-5.40 in addition to a D_2O-exchangeable singlet signal due to an -NH_2 in the region of δ 8.89-9.10. ^{13}C NMR (DMSO-d_6) of **8a-f** revealed an aliphatic -CH_2- carbon signal in the region of δ 56.9-57.38.

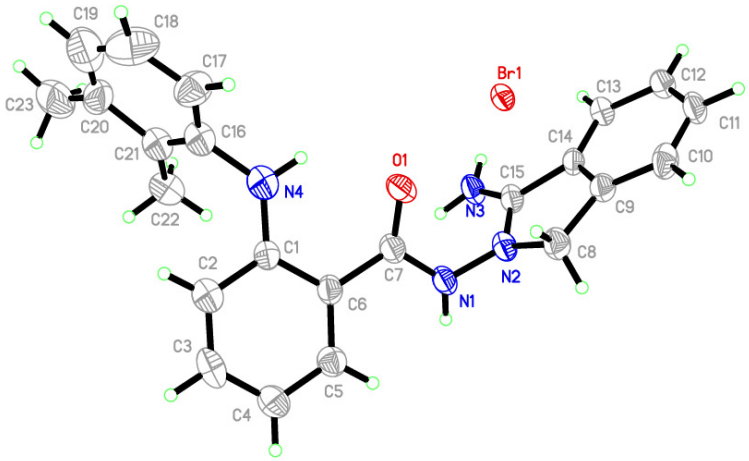


Figure 2. ORTEP diagram of compound **7f**, 50% probability ellipsoid

However, NMR spectra of **8a-f** acquired in MeOD contained the same pattern of signals as in DMSO-d_6. Furthermore, using different protic or aprotic solvents to grow a single crystal of compound **8a** suitable for X-ray analysis resulted in the same structure in the solid state. These results established the complete stable benzenoid unit of 1,2-aza-ylides **8a-f** in the solid state and solution phase.

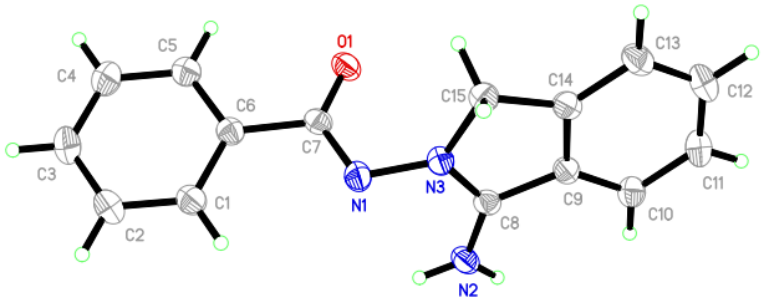


Figure 3. ORTEP diagram of compound **8a**, 50% probability ellipsoid

The above reaction is assumed to proceed *via* the initial reaction of the NH_2 moiety of hydrazides **6a-f** with the bromomethyl branch of **5**, followed by addition of the resulting acyclic quaternary amines **11a-f** to the *ortho*-cyano functionality. The carbon atom of the cyano group becomes C3 of the resulting isoindole skeleton, while the nitrogen atom is converted to the amino group. Reversing the sequence of the latter pathway and the formation of phthalazine **12a-f** are less probable (Scheme 1). However, when we added potassium carbonate to the reaction of **5** with **6a-f**, **8a-f** were obtained in very poor yields (5-12%). The relative stability of 1,2-aza-ylides is somewhat dependent on the substituent pattern. Electron-withdrawing groups stabilise the negative centre, while electron-donating groups stabilise the positive centre.[23] The carbonyl and amino groups play an important role in the formation of the isolable

and stable 1,2-dipole ylene form of ylides **8a-f**. However, NMR and X-ray measurements excluded the formation of **8a-f** or **13a-f** (Figure 4).

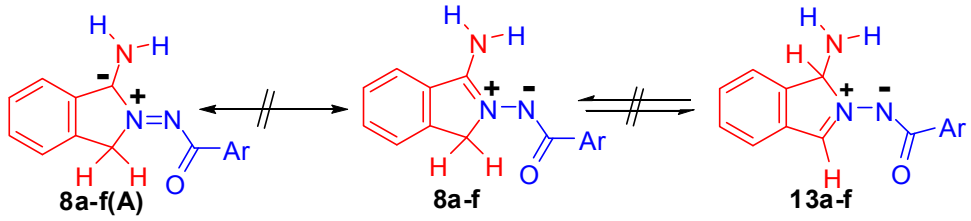


Figure 4. Structure of **8a-f** (A) and **13a-f**

The X-ray analysis measurements of **8a** established the aromaticity of the 1*H*-isoindole moiety, which appeared to be almost planar and had bond lengths in the benzene ring that are within the normal range of an ideal complete benzenoid unit[24] (Figure 5a). The bond lengths for N3-C15 (1.468(2) Å), C8-C9 (1.460(2) Å) and C14-C15 (1.496(2) Å) in the five-membered ring of the 1*H*-isoindole moiety are in the range of single bond lengths, and the bond length of N3-C8 (1.310(2) Å) is in the range of the C_{sp2}=N double bond distance.[24] Moreover, the crystal structure of **8a** is stabilised by an extensive network of intermolecular hydrogen bonds, in which the carbonyl O1 atom is hydrogen bonded to the amino N atom through N2−H1$_{(N2)}$···O1 and N2−H2$_{(N2)}$···O1ii hydrogen bonds (Figure 5b).

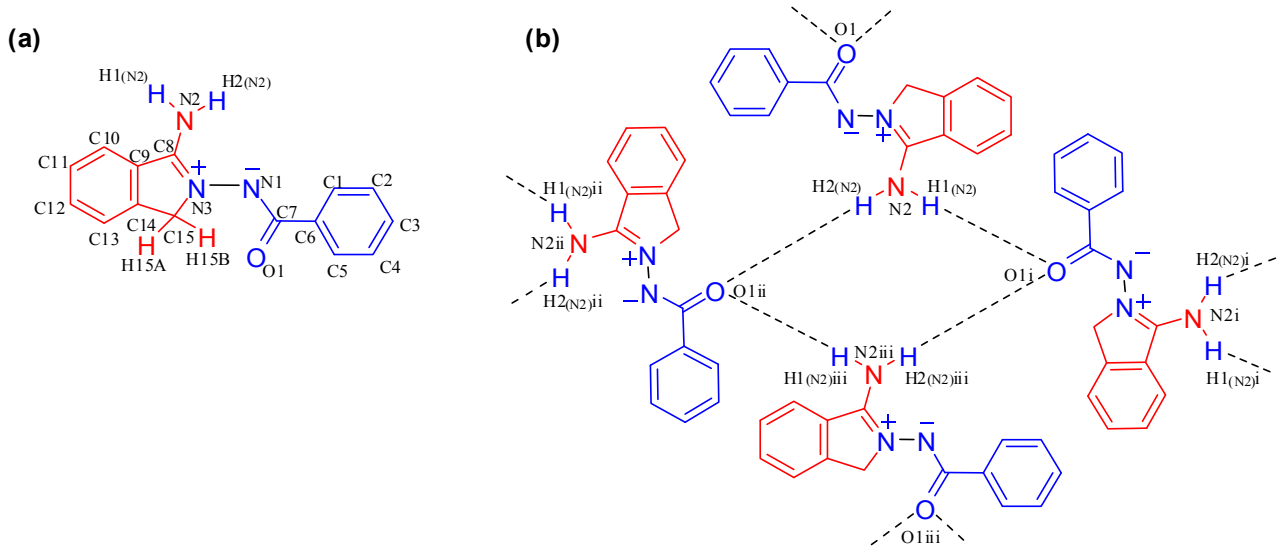
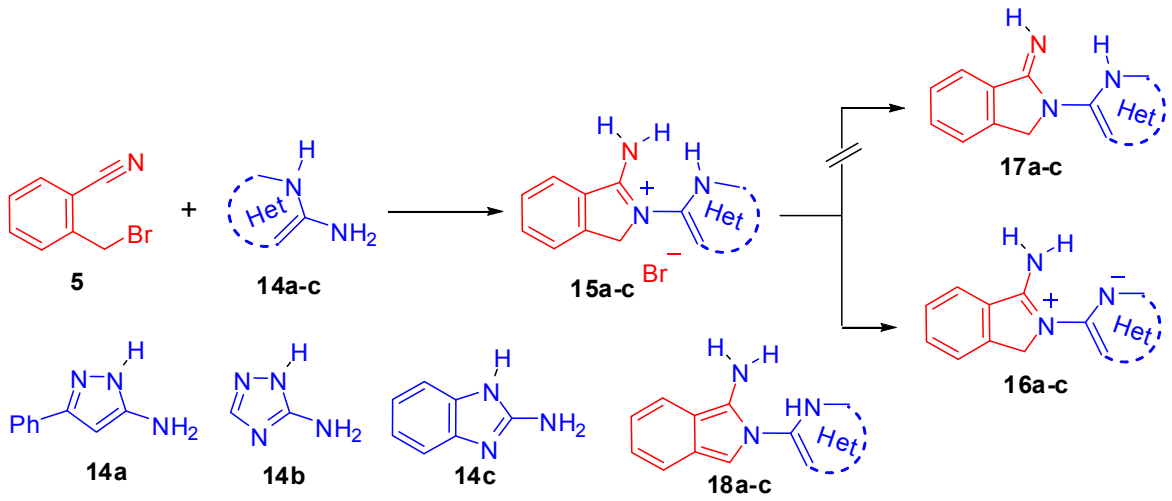


Figure 5a. Labelling of characteristic bond lengths [Å] of **8a**. **Figure 5b**.[25] The geometry of hydrogen bonds for **8a** are represented as dotted lines[26]

Encouraged by the above results, we reacted 2-(bromomethyl)benzonitrile (**5**) with the appropriate heterocyclic amines **14a-c** in a similar manner to give isoindolium bromides **15a-c** (Scheme 2), according to single crystal X-ray analysis of compound **15a**[22] (Figure 6).



Scheme 2. Synthesis of isoindolium 1,3-aza-ylides **16a-c**

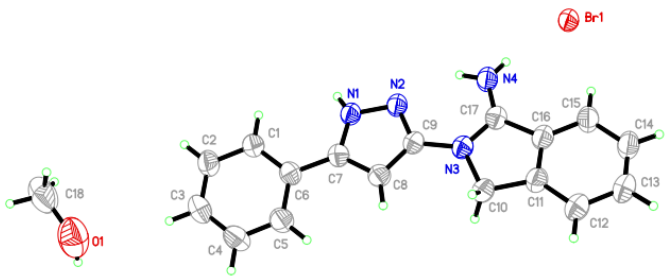


Figure 6. ORTEP diagram of methanol-solvated compound **15a**, 50% probability ellipsoid

Deprotonation of the latter bromide salts **15a-c** yielded their free bases, but trials of growing a single crystal of these free bases failed. However, the 1,3-aza-ylide structures of compounds **16a-c** were confirmed based on their IR and ^{1}H NMR spectra. The IR spectra of the latter compounds exhibited sharp absorption bands due to the quaternary ammonium cation (≡N^{+}-) in the region of 2361-2340 cm^{-1}, while their ^{1}H NMR spectra did not contain the characteristic signal from an NH in a heterocyclic ring (pyrazole, triazole or imidazole) in the region of δ 10-14.[27-29] In addition, the ^{1}H NMR spectra (DMSO-d_6) of **16a-c** contained singlet signals due to methylene protons in the region of δ 5.35-5.66 while their ^{13}C NMR spectra (DMSO-d_6) contained methylene group carbon signals in the region of δ 42.74-55.5. These data excluded the tautomerisation of **16a-c** to their corresponding incomplete

benzenoid structures **18a-c** in the solution phase whereas the appearance of a D_2O-exchangeable signal from the NH_2 group in the region δ 7.21-9.5 excluded structures **17a-c**. However, the azole moiety and amino group supported the formation of 1,3-aza-ylides **16a-c**.[23]

In conclusion, we herein report the convenient synthesis and an interesting configuration of the newly synthesised 1,2- and 1,3-aza-ylides of 1*H*-isoindole in the solid state and solution phase.

EXPERIMENTAL

Infrared (IR) spectra were recorded using KBr disks with the Perkin Elmer FT-IR Spectrum BX apparatus. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were obtained in DMSO-d_6 on a Brucker NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Coupling constants (*J*) are expressed in Hz. D_2O was added to confirm the presence of exchangeable protons. Mass spectra were obtained using a Varian MAT CH-5 spectrometer (70 eV). Elemental analyses were carried out at the Microanalytical Center of Cairo University. The X-ray diffraction measurements were obtained using a Bruker SMART APEX diffractometer. The microwave irradiations were carried out in an Explorer-48 microwave reactor from CEM, USA.

Synthesis of isoindolium bromides 7a-f and 15a-c. A mixture of 2-(bromomethyl)benzonitrile (**5**) (1.96 g, 10 mmol) and the appropriate hydrazide **6a-f** or heterocyclic amine **14a-c** (10 mmol) in absolute MeOH (10 mL) was added to a closed vessel in a microwave reactor. The closed vessel was irradiated with microwaves at 200 W and 90 °C, with 250 psi maximum pressure for 4 min. The vessel was cooled and the solid that formed was collected by filtration and washed with methanol to give isoindolium bromides **7a-f** and **15a-c**, respectively, in 75-92% yields, which were used for the next step without any further purification. Compounds **7a-f** and **15a-c** were synthesized conventionally by refluxing a mixture of **5** (1.96 g, 10 mmol) and the appropriate hydrazide **6a-f** or heterocyclic amine **14a-c** (10 mmol) in absolute MeOH (30 mL) for 10 h and then left to cool. The separated solid was filtered and washed with methanol to give isoindolium bromides **7a-f** and **15a-c**, respectively in 40-68% yields.

3-Amino-2-benzamido-1*H*-isoindolium bromide (7a). White solid, yield (92%); mp 297-299 °C; IR (KBr): *ν* 3450-3075 (NH+NH_2), 2360, 2340 (-C=N^+-), 1669 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 5.34 (s, 2H, CH_2), 7.29-7.40 (m, 3H, ArHs), 7.51-7.58 (m, 1H, ArH), 7.62-7.66 (m, 2H, ArHs), 8.05-8.10 (m, 3H, ArHs), 8.96 (s, D_2O exch., 2H, NH_2), 11.23 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 57.21 ($\underline{C}H_2$), 121.84, 122.81, 127.23, 127.78, 127.87, 128.86, 131.10, 140.29, 154.32, 169.34; EI MS *m/z*: 334 $[M+2]^+$. Anal. Calcd for $C_{15}H_{14}BrN_3O$ (332.20): C, 54.23; H, 4.25; N, 12.65. Found: C, 54.44; H, 4.16; N, 12.79.

3-Amino-2-(4-methylbenzamido)-1*H*-isoindolium bromide (7b). White solid, Yield (85%); mp

327-329 °C; IR (KBr): *v* 3480-3070 (NH+NH_2), 2361, 2340 (-C=N^+-), 1693 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.15 (d, *J* = 7.5 Hz, 2H, ArHs), 7.54-7.64 (m, 1H, ArH), 7.63-7.66 (m, 2H, ArHs), 7.99 (d, *J* = 7.5 Hz, 2H, ArHs), 8.08 (d, *J* = 7.5 Hz, 1H, ArH), 8.98 (s, D_2O exch., 2H, NH_2), 11.47 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.97 ($\underline{C}H_3$), 57.08 ($\underline{C}H_2$), 121.86, 122.80, 127.9, 127.87, 128.65, 131.08, 136.01, 138.35, 140.28, 154.27, 169.83; EI MS *m/z*: 347 $[M+1]^+$. Anal. Calcd for $C_{16}H_{16}BrN_3O$ (346.22): C, 55.51; H, 4.66; N, 12.14. Found: C, 55.74; H, 4.71; N, 12.328.

3-Amino-2-(4-methoxybenzamido)-1*H*-isoindolium bromide (7c). White solid, Yield (82%); mp 325-327 °C; IR (KBr): *v* 3420-3070 (NH+NH_2), 2361, 2339 (-C=N^+-), 1666 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.78 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 6.89 (d, *J* = 7.5 Hz, 2H, ArHs), 7.50-7.58 (m, 1H, ArH), 7.61-7.66 (m, 2H, ArHs), 8.0-8.05 (m, 3H, ArHs), 8.94 (s, D_2O exch., 2H, NH_2), 11.87 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.05 ($\underline{C}H_3$), 56.78 ($\underline{C}H_2$), 112.50, 121.85, 123.11, 127.65, 128.49, 130.54, 131.12, 140.21, 154.56, 159.98, 169.75; EI MS *m/z*: 364 $[M+2]^+$. Anal. Calcd for $C_{16}H_{16}BrN_3O_2$ (362.22): C, 53.05; H, 4.45; N, 11.60. Found: C, 52.93; H, 4.42; N, 11.74.

3-Amino-2-(4-chlorobenzamido)-1*H*-isoindolium bromide (7d). White solid, yield (84%); mp 358-360 °C; IR (KBr): *v* 3430-3060 (NH+NH_2), 2361, 2339 (-C=N^+-), 1668 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.33 (s, 2H, CH_2), 7.39 (d, *J* = 7.5 Hz, 2H, ArHs), 7.50-7.60 (m, 1H, ArH), 7.62-7.64 (m, 2H, ArHs), 8.05-8.08 (m, 1H, ArH), 8.12 (d, *J* = 7.5 Hz, 2H, ArHs), 8.94 (s, D_2O exch., 2H, NH_2), 11.91 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.11 ($\underline{C}H_2$), 121.54, 122.74, 127.16, 128.12, 128.31, 129.63, 131.27, 133.41, 138.72, 141.02, 154.17, 169.84; EI MS *m/z*: 368 $[M+2]^+$. Anal. Calcd for $C_{15}H_{13}BrClN_3O$ (366.64): C, 49.14; H, 3.57; N, 11.46. Found: C, 48.98; H, 3.56; N, 11.54.

3-Amino-2-(4-nitrobenzamido)-1*H*-isoindolium bromide (7e). Pale yellow solid, yield (75%); mp 300-302 °C; IR (KBr): *v* 3375-3090 (NH+NH_2), 2361, 2340 (-C=N^+-), 1698 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.38 (s, 2H, CH_2), 7.50-7.59 (m, 1H, ArH), 7.61-7.70 (m, 2H, ArHs), 8.02-8.04 (m, 1H, ArH), 8.21 (d, *J* = 8.5 Hz, 2H, ArHs), 8.32 (d, *J* = 8.5 Hz, 2H, ArHs), 9.11 (s, D_2O exch., 2H, NH_2), 11.32 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.10 ($\underline{C}H_2$), 122.13, 122.63, 123.21, 128.14, 128.89, 131.40, 140.39, 146.20, 147.62, 154.13, 169.46; EI MS *m/z*: 379 $[M+1]^+$. Anal. Calcd for $C_{15}H_{13}BrN_4O_3$ (377.19): C, 47.76; H, 3.47; N, 14.85. Found: C, 47.69; H, 3.55; N, 14.93.

3-Amino-2-(2-(2,3-dimethylphenylamino)benzamido)-1*H*-isoindolium bromide (7f). Colorless crystals, yield (85%); mp 311-313 °C; IR (KBr): *v* 3445-3060 (2NH+NH_2), 2361, 2340 (-C=N^+-), 1669 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 6.66-6.70 (m, 1H, ArH), 6.80-6.82 (m, 1H, ArH), 6.97-7.05 (m, 2H, ArHs), 7.14-7.21 (m, 2H, ArHs), 7.57-7.60 (m, 1H, ArH), 7.60-7.71 (m, 2H, ArHs), 8.10 (d, *J* = 7.5 Hz, 1H, ArH), 8.34 (d, *J* = 7.5 Hz, 1H,

ArH), 9.13 (s, D_2O exch., 2H, NH_2); 10.84 (s, D_2O exch., 1H, NH), 11.39 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.76 (CH_3), 20.37 (CH_3), 57.23 ($\underline{C}H_2$), 113.42, 116.26, 117.20, 122.02, 122.30, 122.89, 123.32, 125.46, 127.95, 128.49, 129.72, 131.21, 131.38, 137.76, 140.43, 140.71, 145.29, 154.45, 170.99; EI MS *m/z*: 453 $[M+2]^+$. Anal. Calcd for $C_{23}H_{23}BrN_4O$ (451.36): C, 61.20; H, 5.14; N, 12.41. Found: C, 61.01; H, 5.03; N, 12.43.

3-Amino-2-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-isoindolium bromide (15a). Colorless crystals, yield (75%); mp 340-342 °C; IR (KBr): *v* 3380-3000 ($NH+NH_2$), 2361, 2339 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.35 (s, 2H, CH_2), 7.08 (s, 1H, pyrazole), 7.42-7.24 (m, 3H, ArHs), 7.66-7.68 (m, 1H, ArH), 7.81-7.89 (m, 4H, ArHs), 8.41 (d, J = 7.5 Hz, 1H, ArH), 9.12 (s, D_2O exch., 2H, NH_2), 13.20 (s, D_2O exch., H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.01 ($\underline{C}H_2$), 93.84, 123.42, 123.94, 125.51, 128.65, 129.05, 129.43, 133.74, 141.36, 143.82, 148.34, 159.15; EI MS *m/z*: 357 $[M+2]^+$. Anal. Calcd for $C_{17}H_{15}BrN_4$ (355.23): C, 57.48; H, 4.26; N, 15.77. Found: C, 57.55; H, 4.29; N, 15.68.

3-Amino-2-(1*H*-1,2,4-triazol-5-yl)-1*H*-isoindolium bromide (15b). White solid, yield (75%); mp 255-257 °C; IR (KBr): *v* 3320-3050 ($NH+NH_2$), 2361, 2339 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.64 (s, 2H, CH_2), 7.47-7.58 (m, 1H, ArH), 7.69-7.80 (m, 2H, ArHs), 7.89-7.94 (m, 1H, ArH), 8.72 (s, 1H, triazole), 8.91 (s, D_2O exch., 2H, NH_2), 12.75 (s, D_2O exch., H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 53.76 ($\underline{C}H_2$), 111.66, 117.32, 124.00, 127.93, 130.98, 133.57, 138.81, 144.08, 159.36; EI MS *m/z*: 282 $[M+2]^+$. Anal. Calcd for $C_{10}H_{10}BrN_5$ (280.12): C, 42.88; H, 3.60; N, 25.00. Found: C, 42.75; H, 3.63; N, 24.92.

3-Amino-2-(1*H*-benzo[*d*]imidazol-2-yl)-1*H*-isoindolium bromide (15c). White solid, yield (88%); mp 308-310 °C; IR (KBr): *v* 3290-3050 ($NH+NH_2$), 2361, 2340 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.33 (s, 2H, CH_2), 6.86-6.88 (m, 2H, ArHs), 6.95 (s, D_2O exch., 2H, NH_2), 7.48-7.68 (m, 3H, ArHs), 7.90-7.94 (m, 2H, ArHs), 12.17 (s, D_2O exch., H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 45.65 ($\underline{C}H_2$), 108.87, 111.46, 117.43, 120.62, 127.54, 127.94, 131.87, 133.45, 142.23, 155.54; EI MS *m/z*: 331 $[M]^+$. Anal. Calcd for $C_{15}H_{13}BrN_4$ (329.19): C, 54.73; H, 3.98; N, 17.02. Found: C, 45.71; H, 4.59; N, 16.93.

Synthesis of isoindolium ylides 8a-f and 16a-c. An aqueous solution of sodium carbonate (10%, 15 mL) was added to a solution of the appropriate isoindolium bromide **7a-f** or **15a-c** (1 mmol) in distilled water (15 mL). The reaction mixture was stirred for 24 h. The formed precipitate was filtered off, washed with distilled water, dried and recrystallised from EtOH/DMF to give ylides **8a-f** and **16a-c**, respectively.

(3-Amino-1*H*-isoindolium-2-yl)(benzoyl)amide (8a). Colorless crystals, yield (63%); mp 230-232 °C; IR (KBr): *v* 3405, 3052 (NH_2), 2361, 2340 (-C=N^+-), 1677 (C=O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.32 (s, 2H, CH_2), 7.30-7.40 (m, 3H, ArHs), 7.50-7.60 (m, 1H, ArH), 7.64-7.67 (m, 2H, ArHs),

8.07-8.11 (m, 3H, ArHs), 9.01 (s, D_2O exch., 2H, NH_2); ^{1}H NMR (500 MHz, MeOD): δ 5.15 (s, 2H, CH_2), 7.41-7.45 (m, 3H, ArHs), 7.56-7.59 (m, 1H, ArH), 7.67-7.71 (m, 2H, ArHs), 7.98-8.00 (m, 1H, ArHs), 8.07-8.08 (m, 2H, ArHs), 8.59 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.22 ($\underline{C}H_2$), 121.84, 122.80, 127.21, 127.80, 127.87, 128.86, 131.12, 140.31, 154.30, 167.64; ^{13}C NMR (125 MHz, MeOD): δ 58.09 ($\underline{C}H_2$), 123.38, 124.12, 128.93, 129.10, 129.46, 129.84, 131.24, 133.40, 138.55, 142.12, 158.60, 174.24; EI MS *m/z*: 251 $[M]^+$. Anal. Calcd for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.55; H, 5.13; N, 16.49.

(3-Amino-1*H*-isoindolium-2-yl)(4-methylbenzoyl)amide (8b). White solid, Yield (56%); mp 228-230 °C; IR (KBr): *v* 3392, 3047 (NH_2), 2361, 2340 (-C=N$^+$-), 1699 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 7.15 (d, J = 7.5 Hz, 2H, ArHs), 7.55-7.64 (m, 1H, ArH), 7.63-7.65 (m, 2H, ArHs), 7.98 (d, J = 7.5 Hz, 2H, ArHs), 8.05 (d, J = 7.5 Hz, 1H, ArH), 9.00 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.95 ($\underline{C}H_3$), 57.10 ($\underline{C}H_2$), 121.86, 122.81, 127.81, 127.87, 128.66, 131.14, 135.95, 138.35, 140.28, 154.31, 167.63; EI MS *m/z*: 266 $[M+1]^+$. Anal. Calcd for $C_{16}H_{15}N_3O$ (265.31): C, 72.43; H, 5.70; N, 15.84. Found: C, 72.71; H, 5.52; N, 16.03.

(3-Amino-1*H*-isoindolium-2-yl)(4-methoxybenzoyl)amide (8c). White solid, Yield (47%); mp 235-237 °C; IR (KBr): *v* 3385, 3064 (NH_2), 2361, 2340 (-C=N$^+$-), 1676 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 6.89 (d, J = 7.5 Hz, 2H, ArHs), 7.50-7.60 (m, 1H, ArH), 7.62-7.66 (m, 2H, ArHs), 8.00-8.05 (m, 3H, ArHs), 8.90 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.05 ($\underline{C}H_3$), 56.97 ($\underline{C}H_2$), 112.52, 121.86, 122.82, 127.87, 128.80, 129.33, 131.12, 140.23, 154.50, 160.19, 167.42; EI MS *m/z*: 281 $[M]^+$. Anal. Calcd for $C_{16}H_{15}N_3O_2$ (281.31): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.47; H, 5.43; N, 15.15.

(3-Amino-1*H*-isoindolium-2-yl)(4-chlorobenzoyl)amide (8d). White solid, yield (80%); mp 255-257 °C; IR (KBr): *v* 3389, 3067 (NH_2), 2361, 2340 (-C=N$^+$-), 1676 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.35 (s, 2H, CH_2), 7.39 (d, J = 8.0 Hz, 2H, ArHs), 7.50-7.60 (m, 1H, ArH), 7.63-7.66 (m, 2H, ArHs), 8.06-8.08 (m, 1H, ArH), 8.10 (d, J = 8.0 Hz, 2H, ArHs), 8.97 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.35 ($\underline{C}H_2$), 121.83, 122.81, 127.15, 127.92, 128.31, 129.63, 131.20, 133.41, 138.38, 140.34, 153.71, 166.37; EI MS *m/z*: 286 $[M+1]^+$. Anal. Calcd for $C_{15}H_{12}ClN_3O$ (285.73): C, 63.05; H, 4.23; N, 14.71. Found: C, 63.20; H, 4.26; N, 14.89.

(3-Amino-1*H*-isoindolium-2-yl)(4-nitrobenzoyl)amide (8e). Pale yellow solid, yield (78%); mp 266-268 °C; IR (KBr): *v* 3308, 3115 (NH_2), 2361, 2340 (-C=N$^+$-), 1697 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.40 (s, 2H, CH_2), 7.50-7.60 (m, 1H, ArH), 7.60-7.70 (m, 2H, ArHs), 8.02-8.03 (m, 1H, ArH), 8.21 (d, J = 8.5 Hz, 2H, ArHs), 8.34 (d, J = 8.5 Hz, 2H, ArHs), 9.10 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 57.38 ($\underline{C}H_2$), 121.94, 122.52, 122.89, 128.00, 128.89, 131.41, 140.39,

146.20, 147.64, 153.94, 167.60; EI MS *m/z*: 297 $[M+1]^+$. Anal. Calcd for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.63; H, 4.10; N, 19.13.

(3-Amino-1*H*-isoindolium-2-yl)(2-(2,3-dimethylphenylamino)benzoyl)amide (8f). White solid, yield (82%); mp 213-215 °C; IR (KBr): *v* 3404-3066 (NH+NH_2), 2362, 2340 (-C=N^+-), 1672 (C=O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.16 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 6.66-6.69 (m, 1H, ArH), 6.80-6.82 (m, 1H, ArH), 6.97-7.04 (m, 2H, ArHs), 7.13-7.20 (m, 2H, ArHs), 7.57-7.59 (m, 1H, ArH), 7.6-7.7 (m, 2H, ArHs), 8.10 (d, *J* = 7.0 Hz, 1H, ArH), 8.34 (d, *J* = 7.0 Hz, 1H, ArH), 9.00 (s, D_2O exch., 2H, NH_2); 10.86 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.74 (CH_3), 20.37 (CH_3), 57.21 ($\underline{C}H_2$), 113.39, 116.26, 117.22, 121.98, 122.30, 122.88, 123.32, 125.46, 127.95, 128.47, 129.51, 130.76, 131.38, 137.23, 140.40, 140.71, 145.29, 154.21, 170.84; EI MS *m/z*: 370 $[M+1]^+$. Anal. Calcd for $C_{23}H_{22}N_4O$ (370.45): C, 74.57; H, 5.99; N, 15.12. Found: C, 74.53; H, 6.07; N, 15.04.

5-(3-Amino-1*H*-isoindolium-2-yl)-3-phenylpyrazol-1-ide (16a). White solid, yield (75%); mp 255-257 °C; IR (KBr): *v* 3248-2965 (NH_2), 2360, 2337 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.35 (s, 2H, CH_2), 7.07 (s, 1H, pyrazole), 7.44-7.25 (m, 3H, ArHs), 7.66-7.68 (m, 1H, ArH), 7.80-7.88 (m, 4H, ArHs), 8.40 (d, *J* = 7.5 Hz, 1H, ArH), 9.50 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.50 ($\underline{C}H_2$), 93.66, 123.43, 123.94, 125.51, 128.70, 128.99, 129.11, 133.62, 141.32, 143.70, 148.02, 159.34; EI MS *m/z*: 274 $[M]^+$. Anal. Calcd for $C_{17}H_{14}N_4$ (274.32): C, 74.43; H, 5.14; N, 20.42. Found: C, 74.29; H, 5.11; N, 20.57.

5-(3-Amino-1*H*-isoindolium-2-yl)-1,2,4-triazol-1-ide (16b). White solid, yield (45%); mp 146-148 °C; IR (KBr): *v* 3200-3067 (NH_2), 2361, 2340 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.66 (s, 2H, CH_2), 7.47-7.58 (m, 1H, ArH), 7.69-7.79 (m, 2H, ArHs), 7.89-7.94 (m, 1H, ArH), 8.71 (s, 1H, triazole), 8.85 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 50.58 ($\underline{C}H_2$), 111.27, 117.08, 123.30, 127.89, 130.98, 133.31, 138.81, 144.08, 159.33; EI MS *m/z*: 199 $[M]^+$. Anal. Calcd for $C_{10}H_9N_5$ (199.21): C, 60.29; H, 4.55; N, 35.16. Found: C, 60.30; H, 4.52; N, 35.00.

2-(3-Amino-1*H*-isoindolium-2-yl)benzo[*d*]imidazol-1-ide (16c). White solid, yield (66%); mp 160-162 °C; IR (KBr): *v* 3347-3247 (NH_2), 2361, 2340 (-C=N^+-) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 5.35 (s, 2H, CH_2), 6.87-6.88 (m, 2H, ArHs), 7.21 (s, D_2O exch., 2H, NH_2), 7.47-7.66 (m, 3H, ArHs), 7.90-7.92 (m, 2H, ArHs); ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.74 ($\underline{C}H_2$), 106.52, 110.35, 117.28, 120.67, 127.06, 128.04, 131.39, 133.28, 140.93, 152.77; EI MS *m/z*: 248 $[M]^+$. Anal. Calcd for $C_{15}H_{12}N_4$ (248.28): C, 72.56; H, 4.87; N, 22.57. Found: C, 72.39; H, 4.82; N, 22.39.

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22. Crystallographic data for compounds **7f**, **8a** and **15a** have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the numbers 940242, 940380-940381 and 940108-940109, respectively. Copies of the data can be obtained, free of charge, by application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail:

deposit@ccdc.cam.ac.uk http://www.ccdc.cam.ac.uk].

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25. Bond lengths [Å] of the 1*H*-isoindole benzene ring: C9-C10, 1.386(2); C9-C14, 1.391(2); C10-C11, 1.381(2); C11-C12, 1.386(2); C12-C13, 1.387(2); C13-C14, 1.383(2). Bond lengths [Å] of the 1*H*-isoindole five-membered ring: C8-N2, 1.320(2); N2-$H1_{(N2)}$, 0.86(2); N2-$H2_{(N2)}$, 0.93(2); N3-C8, 1.310(2); N3-C15, 1.468(2); C8-C9, 1.460(2); C14-C15, 1.496(2), C15-H15A, 0.99(2); C15-H15B, 0.98(2). Bond lengths [Å] of the benzamide branch: C1-C2, 1.381(2); C1-C6, 1.388(2); C2-C3, 1.376(2); C3-C4, 1.376(3); C4-C5, 1.382(2); C5-C6, 1.390(2); C6-C7, 1.504(2); O1-C7, 1.260(2); N1-N3, 1.409(2); C7-N1, 1.326(2).
26. Distances D—H, H---A and D---A are given in Å, and angles in °. D: donor, and A: acceptor. Intermolecular hydrogen bond D−H---A: D−H Å; H---A Å; D−A Å; <DHA^{o} = N2−$H1_{(N2)}$---O1i: 0.93(2); 1.973; 2.891; 166.83 and N2−$H2_{(N2)}$---O1ii: 0.86(2); 2.187; 2.817; 129.69.
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