

A new protocol for the synthesis of primary, secondary and tertiary anthranilamides utilizing *N*-(2-aminoarylacyl)benzotriazoles

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DOI: <http://dx.doi.org/10.3998/ark.5550190.0013.818>

Abstract

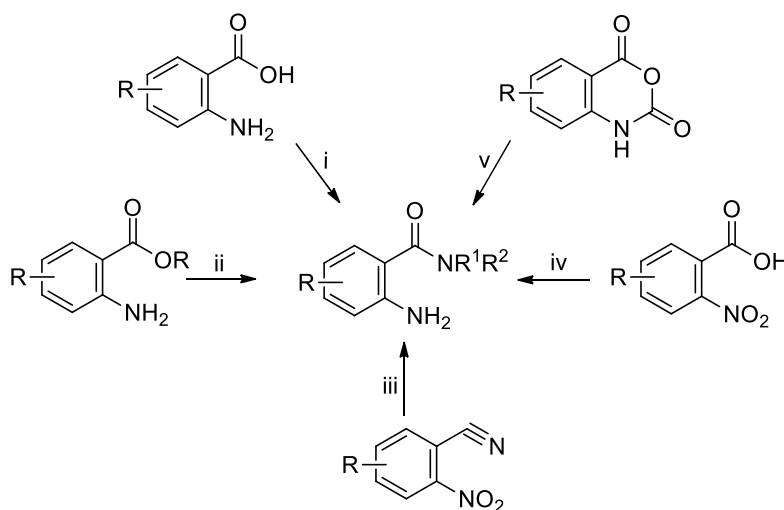
A convenient route for efficient conversion of unprotected anthranilic acids into the corresponding *N*-(2-aminoarylacyl)benzotriazoles is described. *N*-(2-Aminoarylacyl)-benzotriazoles have been successfully used to synthesize primary, secondary and tertiary anthranilamides in high yields (71-96%).

Keywords: Anthranilic acid, benzotriazole, *N*-(2-aminoarylacyl)benzotriazoles, anthranilamides

Introduction

Amides are of great importance in synthetic organic chemistry because of the numerous natural products (e.g. peptides and proteins) and potential drug compounds that contain amide bond, like acetaminophen, an analgesic; lidocaine (Xylocaine), a local anaesthetic and loperamide (Imodium AD), an anti-diarrheal. Amides are also used in different areas of industry¹ (e.g. plastic and rubber industry, and paper industry). As a consequence, much effort has been put onto synthesize new derivatives of amides using mild ways. Anthranilamides are an example of useful compounds containing amide bond since they are used as a starting compound or an intermediate in the synthesis of biologically important compounds such as quinazolones,² quinazolinones^{3a-c} and benzoxazinones.^{3c,4} In addition, some amide derivatives of anthranilic acid show biological activities⁵ or they are the starting materials for *o*-aminonitriles which are versatile synthons to get some useful heterocycles.⁶ Literature methods for synthesizing anthranilamides are: (i) the reaction of anthranilic acid with amine in the presence of various reagents (SOCl₂,^{7a} EDC / HOBt,^{7b} CDI,^{7c} BAC,^{7d} HOSu / DCC,^{7e} DCC / HOBt^{7f}) (ii) the reaction of anthranilesters with amines,⁸ (iii) the catalytically reduction of 2-nitrobenzitriles,⁹ (iv) the reaction of 2-nitrobenzoic acid activated by SOCl₂ with an amine, and then catalytically reduction of nitro group,^{7f,10} and (v) the reaction of isatoic anhydride with various amines^{7c,f,11,12} (Scheme 1). These methods developed to get anthranilamides have some disadvantages like being lack of wide generality in

use, having harsh reaction conditions or complex reaction steps. Conventional activation of a carboxyl group using thionyl chloride cannot be safely employed in the presence of a free amino group.^{7a} The reactions having coupling reagents require anhydrous reaction conditions and activated anthranilic acid intermediates cannot usually be stored, handled in moist air or isolated.^{7b, e, f} In addition, the method including CDI coupling with amine needs using of phosgene in the preparation of CDI.^{7c} The reaction of anthranilesters with amines, on the other hand, requires harsh reaction conditions.⁸ Moreover, the synthesis of anthranilamides from 2-nitrobenzonitriles involves the reduction of nitro group and the hydrolysis of nitrile group. The difficulty in purification of the products cause low yields.⁹ The synthesis of anthranilamides from 2-nitro benzoic acids also has some disadvantages like the difficulty in activation of carboxylic acid group with thionyl chloride and purification of products obtained by the reduction of nitro group.¹⁰ The reaction of isatoic anhydride with amine is a well-known general method for the preparation of anthranilamides. However, this method requires handling of phosgene in the preparation of isatoic anhydride.¹¹ Therefore, newer and versatile methods having simple reaction procedure and reagents to prepare these compounds would be advantageous.



Scheme 1. Literature methods for synthesizing anthranilamides.

Being one of the versatile benzotriazole intermediates, *N*-acylbenzotriazoles have found wide application in the acylation of various nucleophiles because of the good leaving ability of benzotriazole group. They are widely employed in heterocyclic synthesis,^{13a, b} *N*-acylation,^{14a- c} *C*-acylation,^{14b, 15a, b} *S*-acylation^{14b, 16a, b} and *O*-acylation.¹⁷ Unlike the conventional acylating agents which are unstable to moisture and difficult to prepare and store at room temperature, *N*-acylbenzotriazoles are stable crystalline compounds and they are easy to use and store at room temperature.^{14a, 18} They can be prepared directly from carboxylic acids even in cases where an acid sensitive functionality is present. In literature, *N*-acylbenzotriazoles are synthesized from the reaction of carboxylic acids (i) with 1-(methylsulfonyl)benzotriazole in the presence of

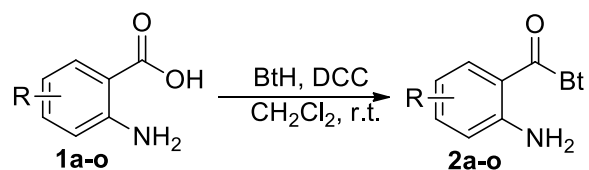
triethylamine^{14a} or (ii) with the excess amount of benzotriazole in the presence of thionylchloride¹⁹ and from the reaction of various aldehydes with *N*-chlorobenzotriazole.²⁰ So far today, various *N*-acylbenzotriazole derivatives have been synthesized from alkyl-, aryl-, heterocyclic- and unsaturated carboxylic acids or carboxylic acids with different functionality. However, there have been no reported studies on the direct synthesis of *N*-acylbenzotriazoles using anthranilic acids. Anthranilic acid component has two different functional groups (COOH and NH₂). The presence of a free amino group makes the activation of carboxylic group difficult and decreases the yield. Therefore, the protection and subsequent deprotection of amino group are necessary to regenerate the amine functionality. However, the use of protecting groups has some drawbacks, like being not economical and causing time loss.

We now report a mild one pot procedure for efficient conversion of anthranilic acids into the corresponding *N*-acylbenzotriazoles having free amino group and subsequent reaction of *N*-acylbenzotriazoles with ammonia, primary and secondary amines to afford substantial anthranilamides.

Results and Discussion

As mentioned before, *N*-acylbenzotriazoles are highly efficient acylating agents to prepare various kinds of compounds comparing to the conventional acylating agents which are mostly sensitive to air and so, difficult to prepare and store at room temperature. Moreover, as an auxiliary group benzotriazole can be recovered almost quantitatively after the reaction. Therefore, this method has also the potential of recycling the starting material.

In the present work, anthranilic acid derivatives were successfully converted into the corresponding *N*-acylbenzotriazoles in the presence of free amino group (Scheme 2). Activation of anthranilic acid with benzotriazole was succeeded by using mild DCC coupling condition. The presence of ortho-substituted free amine functionality in the molecules did not cause any troubles except for **2e** and **2f**. The resulting compounds **2a-o** were successfully isolated and purified by column chromatography as stable, yellow colored solids in 14 – 93% yields (Table 1). All of the *N*-acylbenzotriazole derivatives prepared are novel compounds and structures of products **2a-o** were fully characterized by IR, ¹H NMR and ¹³C NMR spectroscopy. Elemental analysis and mass spectroscopy also supported the proposed structures. The most characteristic ¹H-NMR data indicating that benzotriazole attached to the molecules are the signals which were observed for the protons on the benzotriazole ring as doublets at 8.37 – 8.17 ppm and as triplets at 7.69 – 7.55 ppm. In addition to the ¹H-NMR spectral data, 12 signals were observed for the carbons in aromatic rings of the products in the ¹³C-NMR spectra.



Scheme 2. Synthesis of *N*-(2-aminoarylacyl)benzotriazoles (**2a-o**).

Table 1. Synthesized *N*-(2-aminoarylacyl)benzotriazoles **2a-o** from the proposed method

	R	Yield (%)	Mp (°C)		R	Yield (%)	Mp (°C)
a	H	78	132 – 133	i	5-bromo	53	174 – 176
b	3-methyl	82	99 – 100	j	5-iodo	55	138 – 140
c	4-methyl	76	135 – 136	k	3,5-dichloro	93	170 – 172
d	5-methyl	40	104 – 106	l	3,5-dibromo	83	174 – 176
e	6-methyl	25	106 – 108	m	3,5-diiodo	64	decomposed > 220
f	5-methoxy	14	107 – 109	n	4,5-dimethoxy	70	93 – 95
g	4-chloro	92	160 – 162	o	3,4,5-trimethoxy	75	115 – 117
h	5-chloro	74	153 – 155				

During the preparation of *N*-(2-aminoarylacyl)benzotriazoles **2a-o**, it was noticed that a by-product **2'** (Figure 1) was formed with the desired products because of the nature and position of the substituents in the corresponding anthranilic acids. The yields of by-products were almost negligible except for **2e** and **2f**. The by-products **2e'** and **2f'** were isolated by column chromatography in 27 % and 42 yields respectively. Their structures were supported by ¹H and ¹³C NMR spectra. The expected signals which belong to benzotriazole ring weren't observed in ¹H and ¹³C NMR spectra. Moreover, for the two carbonyl carbons in the structures, two signals were observed in ¹³C NMR spectra. MS spectra also support the structures of these side products. Steric hindrance of the methyl group, which is in ortho position to the carboxylic acid, caused the low yield of the desired product **2e**. In case of **2f**, the methoxy group present in para position to amino group increased nucleophilicity of amino group and caused the formation of by-product.

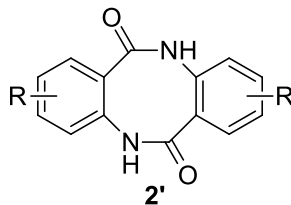
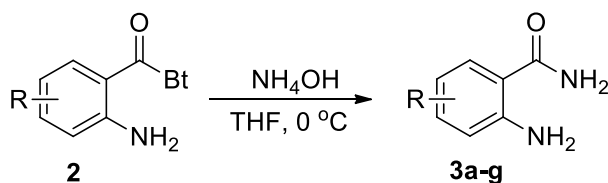


Figure 1. The by-product produced during the activation of anthranilic acids with benzotriazole.

The reaction of *N*-(2-aminoarylacyl)benzotriazoles with ammonia, various primary and secondary amines gives primary, secondary and tertiary anthranilamides. In spite of having free amino groups, no complications were observed and the reactions were rather straight forward. Therefore, anthranilamides were synthesized in high yields (71-96%). Spectroscopic studies have provided strong evidence that amides formed. Especially, the disappearance of the benzotriazole signals in the aromatic region of $^1\text{H-NMR}$ spectra indicates the loss of the benzotriazolyl group during the reaction and shows the formation of amides. Characteristic amide peaks were observed for all compounds on IR spectra. Moreover, mass spectra show that the expected molecular ion and the fragmentation are in accordance with the proposed structures.

Primary anthranilamides were efficiently synthesized by treatment of *N*-acylbenzotriazoles with excess ammonium hydroxide (27% aqueous solution) in THF at 0 °C for 2 hours (Scheme 3). The products were isolated by column chromatography in 82-96% yields (Table 2) and characterized spectrally and by elemental analyses. The $^1\text{H-NMR}$ spectrum showed two broad signals for each proton of amino groups attached to the carbonyl group at 8.06-7.58 ppm and 7.47-6.44 ppm, which are in agreement with the reported values for these types of compounds.^{21a,b} Similarly, the signals in the $^{13}\text{C-NMR}$ spectra for carbonyl carbons were observed at 172.8-170.5 ppm, apart from six carbon signals for aromatic ring in the aromatic region. In addition to spectral and elemental analysis, the melting points of the products were measured (Table 2).

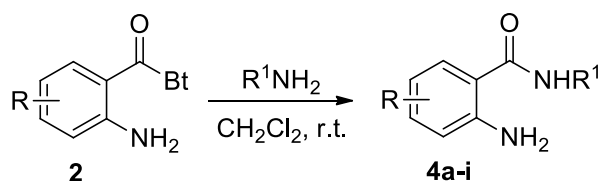


Scheme 3. Synthesis of primary amides (**3a-g**) from *N*-(2-aminoarylacyl)benzotriazoles.

Table 2. Preparation of primary amides **3a-g**

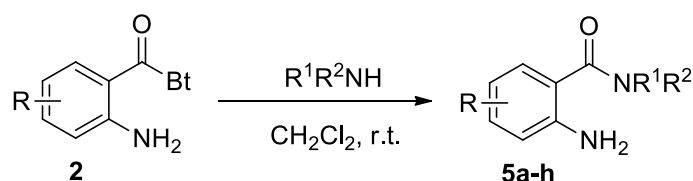
	R	Yield (%)	Lit. Yield (%)	mp (°C)
a	H	96	90 ^(Ref. 22)	112 – 113
b	4-methyl	93	86 ^(Ref. 21b)	148 – 149
c	4-chloro	88	83 ^(Ref. 23)	180 – 182
d	5-bromo	93	100 ^(Ref. 24)	185 – 187
e	5-iodo	89	82 ^(Ref. 25)	177 – 178
f	4,5-dimethoxy	82	100 ^(Ref. 26)	148 – 149
g	3,5-dibromo	85	54 ^(Ref. 27)	214 – 215

Various primary amines were treated with anthranilbenzotriazoles in dichloromethane to give a series of secondary anthranilamides **4a-i** (Scheme 4). The reactions were completed in 2-6 hours at room temperature with high yields (71-95%). The synthesized compounds gave satisfactory proton and carbon NMR data. The most characteristic signal for the secondary amides is the broad singlet which was observed at 6.35-5.82 ppm for the protons of the amide nitrogen atom in ¹H-NMR. Elemental analysis, IR and mass spectroscopy also supported the structures of **4a-i**. The isolated yields, literature yields and observed melting points were summarized in Table 3.

**Scheme 4.** Synthesis of secondary amides (**4a-i**) from *N*-(2-aminoarylacetyl)benzotriazoles.**Table 3.** Preparation of secondary amides **4a-i**

	R	R1	Yield (%)	Lit. Yield (%)	mp (°C)
a	H	benzyl	71	95 ^(Ref. 28)	121 – 122
b	3-methyl	n-propyl	79	65 ^(Ref. 29)	105 – 106
c	4- methyl	cyclohexyl	86	novel	150 – 151
d	5- methyl	cyclohexyl	86	novel	201 – 202
e	5-methoxy	n-propyl	82	novel	72 – 74
f	4-chloro	methyl	93	74 ^(Ref. 30)	96 – 97
g	5-bromo	isopropyl	87	novel	188 – 189
h	3,5-dichloro	n-propyl	95	novel	143 – 144
i	4,5-dimethoxy	methyl	84	80 ^(Ref. 31)	117 – 119

Treatment of *N*-(2-aminoarylacyl)benzotriazoles with secondary amines in CH₂Cl₂ at room temperature gave the corresponding tertiary amides in excellent yields (77-96%) (Scheme 5, Table 4). Structures of the products were confirmed by the results of NMR measurements. The most important evidence proving the formation of tertiary amides is the signals which were observed for the substituents attached to the amide nitrogen atom. Moreover, no broad singlet was observed except for the one accounting for the amino group on the anthranilic acid ring.



Scheme 5. Synthesis of tertiary amides (**5a-h**) from *N*-(2-aminoarylacyl)benzotriazoles.

Table 4. Preparation of Tertiary Amides **5a-h**

	R	R ¹ +R ²	Yield (%)	Lit. yield (%)	mp (°C)
a	H	(-CH ₂) ₅	90	83 (Ref. 31)	74 – 76
b	3-methyl	(-CH ₂) ₅	86	98 (Ref. 31)	80 – 81
c	6- methyl	(-CH ₂) ₄	94	novel	78 – 79
d	5-chloro	(-CH ₂) ₄ O	90	novel	130 – 131
e	5-iodo	(-CH ₂) ₄	89	novel	134 – 135
f	3,5-dibromo	(-CH ₂ CH ₃) ₂	89	novel	oil
g	3,5-diiodo	(-CH ₂) ₄ O	96	novel	128 – 130
h	3,4,5-trimethoxy	(-CH ₂ CH ₃) ₂	93	novel	oil

Conclusions

In conclusion, a series of *N*-(2-aminoarylacyl)benzotriazoles were synthesized from unprotected orthoaminoarylcarboxylic acids. By the treatment of synthesized *N*-(2-aminoarylacyl)benzotriazoles with ammonia, primary and secondary amines, we have developed a new and practical protocol for the synthesis of anthranilamides. Advantages of this method compared to the existing methodologies are: providing neutral reaction conditions for the compounds possessing acid – base sensitive substituents, using *N*-acylbenzotriazoles which are more useful and stable than the corresponding acyl halides or other activated derivatives of carboxylic acids, general application and good yields that are comparable to the literature.

Experimental Section

General. Column chromatography was conducted on silica gel 70 – 230 meshes. Melting points were determined on a Mettler Toledo apparatus and uncorrected. All NMR spectra were recorded on a Bruker Advance 500 DPX spectrometer in CDCl₃ or DMSO-*d*₆ with TMS as the internal reference for ¹H (500 MHz) and ¹³C (125 MHz). Reagents obtained commercially were used without further purification. MS analyses were obtained with a GC–MS/MS (Thermo Finnigan PolarisQ). Elemental analysis was performed for all compounds with a Thermo Finnigan Flash EA 1112 instrument. FTIR spectra were determined on a PerkinElmer 100 FTIR spectrometer.

General experimental procedure for the preparation of *N*-(2-aminoarylacetyl)benzotriazoles (2a-p). A mixture of appropriate anthranilic acid (6 mmol), benzotriazole (5 mmol, 0.595 gr) and DCC (7 mmol, 1.44 gr) was stirred in CH₂Cl₂ (10 mL) overnight at room temperature. After completion of the reaction, the solvent was removed under reduced pressure. Purification of the residue by column chromatography over silica gel with EtOAc/ *n*-Hexane (1:3) or CH₂Cl₂ gave the desired product.

(2-Aminophenyl) (benzotriazole-1-yl)methanone (2a). Yellow solid (0.928 g, 78%); mp 132-133 °C; IR ν_{\max} (KBr) 3476, 3356, 1680 cm⁻¹; ¹H NMR (CDCl₃) δ 8.29 (d, *J* 8.3 Hz, 1H), 8.19 (d, *J* 8.3 Hz, 1H), 8.07 (d, *J* 8.2 Hz, 1H), 7.70 (t, *J* 7.7 Hz, 1H), 7.55 (t, *J* 7.7 Hz, 1H), 7.43 (t, *J* 7.7 Hz, 1H), 6.84 – 6.79 (m, 2H), 5.81 (br s, 2H); ¹³C NMR δ 167.3, 151.9, 145.7, 135.4, 134.3, 132.7, 129.9, 125.9, 120.2, 117.0, 116.5, 114.5, 111.8; MS (EI): *m/z* [M⁺] calcd. for C₁₃H₁₀N₄O: 238.08, found: 238.0; Anal. Calc. for C₁₃H₁₀N₄O: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.63; H, 4.28; N, 23.63.

(2-Amino-3-methylphenyl) (benzotriazole-1-yl)methanone (2b). Yellow solid (1.03 g, 82%); mp 99-100 °C; IR ν_{\max} (KBr) 3473, 3369, 1670 cm⁻¹; ¹H NMR (CDCl₃) δ 8.26 (d, *J* 8.3 Hz, 1H), 8.18 (d, *J* 8.3 Hz, 1H), 7.89 (d, *J* 8.2 Hz, 1H), 7.68 (t, *J* 7.7 Hz, 1H), 7.54 (t, *J* 7.7 Hz, 1H), 7.34 (d, *J* 7.2 Hz, 1H), 6.74 (t, *J* 7.7 Hz, 1H), 5.34 (br s, 2H), 2.25 (s, 3H); ¹³C NMR δ 167.8, 150.3, 145.7, 136.1, 132.7, 132.4, 129.8, 125.9, 123.2, 120.1, 115.8, 114.4, 111.3, 17.5; MS (EI): *m/z* [M⁺] calcd. for C₁₄H₁₂N₄O: 252.10, found: 252.0; Anal. Calc. for C₁₄H₁₂N₄O: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.72; H, 4.92; N, 22.38.

(2-Amino-4-methylphenyl) (benzotriazole-1-yl)methanone (2c). Yellow solid (0.958 g, 76%); mp 135-136 °C; IR ν_{\max} (KBr) 3465, 3351, 1675 cm⁻¹; ¹H NMR (CDCl₃) δ 8.24 (d, *J* 8.3 Hz, 1H), 8.17 (d, *J* 8.3 Hz, 1H), 7.96 (d, *J* 8.3 Hz, 1H), 7.66 (t, *J* 7.7 Hz, 1H), 7.52 (t, *J* 7.6 Hz, 1H), 6.61-6.59 (m, 2H), 6.22 (br s, 2H), 2.36 (s, 3H); ¹³C NMR δ 168.0, 153.4, 147.7, 146.5, 135.0, 133.6, 130.5, 126.5, 120.7, 118.8, 117.7, 115.1, 109.9, 22.0; MS (EI): *m/z* [M⁺] calcd. for C₁₄H₁₂N₄O: 252.10, found: 252.0; Anal. Calc. for C₁₄H₁₂N₄O: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.57; H, 4.76; N, 22.22.

(2-Amino-5-methylphenyl) (1H-benzotriazole-1-yl)methanone (2d). Yellow solid (0.504 g, 40%); mp 104-106 °C; IR ν_{\max} (KBr) 3477, 3367, 1682 cm⁻¹; ¹H NMR (CDCl₃) δ 8.26 (d, *J* 8.3 Hz, 1H), 8.18 (d, *J* 8.3 Hz, 1H), 7.82 (br s, 1H), 7.69 (t, *J* 7.7 Hz, 1H), 7.54 (t, *J* 7.7 Hz, 1H),

7.25 (d, *J* 8.4 Hz, 1H), 6.75 (d, *J* 8.4 Hz, 1H), 5.67 (br s, 2H), 2.29 (s, 3H); ^{13}C NMR δ 168.3, 150.8, 146.6, 137.5, 134.4, 133.5, 130.6, 126.6, 120.8, 117.8, 115.2, 112.5, 20.5; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: 252.10, found: 252.0; Anal. Calc. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: C, 66.65; H, 4.79; N, 22.21. Found: 66.91; H, 4.90; N, 22.25.

(2-Amino-6-methylphenyl) (benzotriazole-1-yl)methanone (2e). Yellow solid (0.315 g, 25%); mp 106-108 °C; IR ν_{max} (KBr) 3436, 3369, 1707 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.37 (d, *J* 8.5 Hz, 1H), 8.18 (d, *J* 8.0 Hz, 1H), 7.73 (t, *J* 8.0 Hz, 1H), 7.58 (t, *J* 8.3 Hz, 1H), 7.26 (t, *J* 7.8 Hz, 1H), 6.73 (d, *J* 7.5 Hz, 1H), 6.70 (d, *J* 8.0 Hz, 1H), 4.14 (br s, 2H), 2.11 (s, 3H); ^{13}C NMR δ 168.9, 146.4, 145.6, 137.5, 132.2, 131.3, 130.5, 126.5, 120.6, 120.4, 119.3, 114.5, 114.4, 20.4; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: 252.10, found: 252.0; Anal. Calc. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.50; H, 4.80; N, 22.43.

(2-Amino-5-methoxyphenyl) (benzotriazole-1-yl)methanone (2f). Yellow solid (0.188 g, 14%); mp 107-109 °C; IR ν_{max} (KBr) 3478, 3371, 1687 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.31 (d, *J* 8.3 Hz, 1H), 8.19 (d, *J* 8.4 Hz, 1H), 7.71 (t, *J* 7.7 Hz, 1H), 7.62 (d, *J* 2.9 Hz, 1H), 7.56 (t, *J* 7.7 Hz, 1H), 7.13 (dd, *J* 9.0, 2.9 Hz, 1H), 6.83 (d, *J* 9.0 Hz, 1H), 5.80 (br s, 2H), 3.80 (s, 3H); ^{13}C NMR δ 166.9, 150.7, 146.3, 145.7, 132.7, 130.0, 126.0, 124.9, 120.1, 118.8, 115.8, 114.6, 112.1, 55.9; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2$: 268.09, found: 268.0; Anal. Calc. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: C, 62.69; H, 4.48; N, 20.9. Found: C, 62.51; H, 4.61; N, 20.89.

(2-Amino-4-chlorophenyl) (benzotriazole-1-yl)methanone (2g). Yellow solid (1.25 g, 92%); mp 160-162 °C; IR ν_{max} (KBr) 3464, 3338, 1687 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.27 (d, *J* 8.2 Hz, 1H), 8.18 (d, *J* 8.2 Hz, 1H), 8.07 (d, *J* 8.7 Hz, 1H), 7.70 (t, *J* 7.6 Hz, 1H), 7.55 (t, *J* 7.7 Hz, 1H), 6.83 (s, 1H), 6.77 (d, *J* 8.7 Hz, 1H), 5.94 (br s, 2H); ^{13}C NMR δ 167.3, 153.6, 146.6, 142.6, 136.6, 133.4, 130.8, 126.8, 120.9, 117.8, 117.0, 115.2, 110.9; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}$: 272.04, found: 272.0; Anal. Calc. for $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}$: C, 57.25; H, 3.33; N, 20.54. Found: C, 57.28; H, 3.40; N, 20.58.

(2-Amino-5-chlorophenyl) (benzotriazole-1-yl)methanone (2h). Yellow solid (1.01 g, 74%); mp 153-155 °C; IR ν_{max} (KBr) 3465, 3333, 1679 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.28 (d, *J* 8.3 Hz, 1H), 8.20 (d, *J* 8.3 Hz, 1H), 8.11 (d, *J* 2.3 Hz, 1H), 7.71 (t, *J* 7.6 Hz, 1H), 7.57 (t, *J* 7.7 Hz, 1H), 7.36 (dd, *J* 8.9, 2.3, 1H), 6.78 (d, *J* 8.9 Hz, 1H), 5.83 (br s, 2H); ^{13}C NMR δ 167.3, 151.3, 146.6, 136.2, 134.0, 133.4, 131.0, 126.9, 121.8, 121.0, 119.1, 115.2, 113.2; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}$: 272.04, found: 271.9; Anal. Calc. for $\text{C}_{13}\text{H}_9\text{ClN}_4\text{O}$: C, 57.25; H, 3.33; N, 20.54. Found: C, 57.36; H, 3.36; N, 20.33.

(2-Amino-5-bromophenyl) (benzotriazole-1-yl)methanone (2i). Yellow solid (0.840 g, 53%); mp 151-153 °C; IR ν_{max} (KBr) 3465, 3330, 1677 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.28 (d, *J* 8.3 Hz, 1H), 8.24 (d, *J* 2.3 Hz, 1H), 8.20 (d, *J* 8.3 Hz, 1H), 7.72 (t, *J* 7.6 Hz, 1H), 7.57 (t, *J* 7.6 Hz, 1H), 7.49 (dd, *J* 8.9, 2.3 Hz, 1H), 6.73 (d, *J* 8.9 Hz, 1H), 5.83 (br s, 2H); ^{13}C NMR δ 166.2, 150.7, 145.7, 138.0, 136.1, 132.5, 130.1, 126.2, 120.3, 118.7, 114.5, 113.1, 107.7; MS (EI): *m/z* [M^+] calcd. for $\text{C}_{13}\text{H}_9\text{BrN}_4\text{O}$: 315.99, found: 315.9; Anal. Calc. for $\text{C}_{13}\text{H}_9\text{BrN}_4\text{O}$: C, 49.23; H, 2.86; N, 17.67. Found: C, 49.27; H, 2.95; N, 17.54.

(2-Amino-5-iodophenyl) (benzotriazole-1-yl)methanone (2j). Yellow solid (1.00 g, 55%); mp 138-140 °C; IR ν_{\max} (KBr) 3489, 3382, 1691 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.34 (d, J 2.0 Hz, 1H), 8.25 (d, J 8.3 Hz, 1H), 8.18 (d, J 8.3 Hz, 1H), 7.70 (t, J 7.7 Hz, 1H), 7.61 (dd, J 8.8, 2.0 Hz, 1H), 7.55 (t, J 7.7 Hz, 1H), 6.61 (d, J 8.8 Hz, 1H), 5.86 (br s, 2H); ^{13}C NMR δ 166.0, 151.2, 145.7, 143.3, 142.0, 132.5, 130.2, 126.2, 120.2, 119.1, 114.5, 113.9, 76.1; MS (EI): m/z [M^+] calcd. for $\text{C}_{13}\text{H}_9\text{IN}_4\text{O}$: 363.98, found: 363.9; Anal. Calc. for $\text{C}_{13}\text{H}_9\text{IN}_4\text{O}$: C, 42.88; H, 2.49; N, 15.39. Found: C, 43.00; H, 2.59; N, 15.17.

(2-Amino-3, 5-dichlorophenyl) (benzotriazole-1-yl)methanone (2k). Yellow solid (1.43 g, 93%); mp 170-172 °C; IR ν_{\max} (KBr) 3486, 3367, 1679 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.30 (d, J 8.2 Hz, 1H), 8.21 (d, J 8.3 Hz, 1H), 8.07 (d, J 2.4 Hz, 1H), 7.74 (t, J 7.7 Hz, 1H), 7.60-7.57 (m, 2H), 6.26 (br s, 2H); ^{13}C NMR δ 166.0, 146.4, 145.8, 134.5, 132.5, 132.2, 130.4, 126.4, 121.2, 120.4, 120.3, 114.6, 113.3; MS (EI): m/z [M^+] calcd. for $\text{C}_{13}\text{H}_8\text{Cl}_2\text{N}_4\text{O}$: 306.00, found: 305.9; Anal. Calc. for $\text{C}_{13}\text{H}_8\text{Cl}_2\text{N}_4\text{O}$: C, 50.65; H, 2.62; N, 18.18. Found: C, 50.87; H, 2.76; N, 17.86.

(2-Amino-3, 5-dibromophenyl) (benzotriazole-1-yl)methanone (2l). Yellow solid (1.64 g, 83%); mp 174-176 °C; IR ν_{\max} (KBr) 3488, 3366, 1608 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.29 (d, J 8.3 Hz, 1H), 8.22 – 8.20 (m, 2H), 7.85 (d, J 2.2 Hz, 1H), 7.74 (t, J 7.7 Hz, 1H), 7.59 (t, J 7.7 Hz, 1H), 6.32 (br s, 2H); ^{13}C NMR δ 165.8, 147.5, 145.8, 140.1, 135.8, 132.5, 130.4, 126.4, 120.4, 114.6, 113.8, 111.5, 106.9; MS (EI): m/z [M^+] calcd. for $\text{C}_{13}\text{H}_8\text{Br}_2\text{N}_4\text{O}$: 393.90, found: 393.8; Anal. Calc. for $\text{C}_{13}\text{H}_8\text{Br}_2\text{N}_4\text{O}$: C, 39.32; H, 2.03; N, 14.11. Found: C, 39.56; H, 2.19; N, 13.78.

(2-Amino-3, 5-diiodophenyl) (benzotriazole-1-yl)methanone (2m). Yellow solid (1.57 g, 64%); mp decomposed > 220 °C; IR ν_{\max} (KBr) 3489, 3375, 1667 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.30 – 8.19 (m, 4H), 7.73 (t, J 7.7 Hz, 1H), 7.59 (t, J 7.7 Hz, 1H), 6.35 (br s, 2H); ^{13}C NMR δ 165.8, 151.6, 149.9, 145.8, 142.6, 132.5, 130.4, 126.4, 120.4, 114.5, 113.8, 87.3, 75.9; MS (EI): m/z [M^+] calcd. for $\text{C}_{13}\text{H}_8\text{I}_2\text{N}_4\text{O}$: 489.87, found: 489.7; Anal. Calc. for $\text{C}_{13}\text{H}_8\text{I}_2\text{N}_4\text{O}$: C, 31.80; H, 1.64; N, 11.41. Found: C, 32.00; H, 1.78; N, 11.33.

(2-Amino-4, 5-dimethoxyphenyl) (benzotriazole-1-yl)methanone (2n). Yellow solid (1.04 g, 70%); mp 93-95 °C; IR ν_{\max} (KBr) 3470, 3361, 1672 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.25 (d, J 8.3 Hz, 1H), 8.17 (d, J 8.3 Hz, 1H), 7.72 (s, 1H), 7.68 (t, J 7.7 Hz, 1H), 7.53 (t, J 7.6 Hz, 1H), 6.27 (s, 1H), 6.05 (br s, 2H), 3.96 (s, 3H), 3.84 (s, 3H); ^{13}C NMR δ 165.9, 156.6, 150.6, 145.5, 140.8, 133.0, 129.6, 125.7, 120.0, 115.0, 114.5, 102.7, 99.0, 56.4, 56.0; MS (EI): m/z [M^+] calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_3$: 298.10, found: 298.0; Anal. Calc. for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.45; H, 4.79; N, 18.89.

(2-Amino-3, 4, 5-trimethoxyphenyl) (benzotriazole-1-yl)methanone (2o). Yellow solid (1.23 g, 75%); mp 115-117 °C; IR ν_{\max} (KBr) 3465, 3342, 1664 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.28 (d, J 8.3 Hz, 1H), 8.18 (d, J 8.3 Hz, 1H), 7.69 (t, J 7.6 Hz, 1H), 7.55 (t, J 7.6 Hz, 1H), 7.52 (s, 1H), 6.08 (br s, 2H), 4.07 (s, 3H), 3.95 (s, 3H), 3.82 (s, 3H); ^{13}C NMR δ 166.3, 148.8, 145.6, 144.0, 143.5, 139.9, 132.9, 129.8, 125.8, 120.0, 114.6, 111.1, 105.2, 61.0, 60.5, 56.4; MS (EI): m/z [M^+] calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4$: 328.11, found: 328.0; Anal. Calc. for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.70; H, 4.93; N, 17.24.

General experimental procedure for the preparation of primary anthranilamides (3a-g). *N*-(2-Aminoarylacetyl)benzotriazoles (1 mmol) were treated with excess ammonium hydroxide (10 mmol) in THF (10 mL) cooled in an ice bath for 2 hours. After the completion of the reaction, the solvent was removed under reduced pressure and then the residue was purified by column chromatography over silica gel with EtOAc/ *n*-Hexane (1:1) to give the desired primary amides as white solids.

2-Aminobenzamide (3a). White solid (0.130 g, 96%); mp 112-113 °C; IR ν_{\max} (KBr) 3409.5, 3316.0, 3201.3, 1660.4 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.74 (br s, 1H), 7.52 (d, J 7.9 Hz, 1H), 7.13 (t, J 7.6 Hz, 1H), 7.06 (br s, 1H), 6.67 (d, J 8.2 Hz, 1H), 6.55 (br s, 2H), 6.48 (t, J 7.5 Hz, 1H); ^{13}C NMR δ 172.8, 151.5, 133.2, 130.0, 117.6, 115.6, 114.8; MS (EI): m/z [M^+] calcd. for $\text{C}_7\text{H}_8\text{N}_2\text{O}$: 136.06, found: 136.0; Anal. Calc. for $\text{C}_7\text{H}_8\text{N}_2\text{O}$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.95; H, 6.28; N, 20.20.

2-Amino-4-methylbenzamide (3b). White solid (0.140 g, 93%); mp 148-149 °C; IR ν_{\max} (KBr) 3409.5, 3294.8, 3172.3, 1674.9 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.65 (br s, 1H), 7.43 (d, J 8.1 Hz, 1H), 6.95 (br s, 1H), 6.54 (br s, 2H), 6.48 (s, 1H), 6.30 (d, J 8.0 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR δ 172.8, 151.7, 143.0, 130.0, 117.7, 116.9, 112.2, 21.7; MS (EI): m/z [M^+] calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$: 150.07, found: 150.0; Anal. Calc. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$: C, 63.98; H, 7.19; N, 18.64. Found: C, 64.21; H, 7.19; N, 18.20.

2-Amino-4-chlorobenzamide (3c). White solid (0.150 g, 88%); mp 180-182 °C; IR ν_{\max} (KBr) 3496.3, 3351.7, 3164.6, 3085.5, 1667.2 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.80 (br s, 1H), 7.54 (d, J 8.4 Hz, 1H), 7.16 (br s, 1H), 6.83 (br s, 2H), 6.74 (s, 1H), 6.50 (t, J 8.4 Hz, 1H); ^{13}C NMR δ 172.0, 152.8, 137.6, 131.8, 116.3, 115.2, 113.5; MS (EI): m/z [M^+] calcd. for $\text{C}_7\text{H}_7\text{ClN}_2\text{O}$: 170.02, found: 170.0; Anal. Calc. for $\text{C}_7\text{H}_7\text{ClN}_2\text{O}$: C, 49.27; H, 4.13; N, 16.42. Found: C, 49.18; H, 4.48; N, 16.06.

2-Amino-5-bromobenzamide (3d). White solid (0.200 g, 93%); mp 185-187 °C; IR ν_{\max} (KBr) 3395.1, 3287.1, 3164.6, 1674.9 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.86 (br s, 1H), 7.70 (d, J 2.5 Hz, 1H), 7.26 (dd, J 9.0, 2.0 Hz, 1H), 7.19 (br s, 1H), 6.71 (br s, 2H), 6.66 (d, J 8.5 Hz, 1H); ^{13}C NMR δ 170.5, 149.8, 134.8, 131.2, 119.0, 115.6, 105.2; MS (EI): m/z [M^+] calcd. for $\text{C}_7\text{H}_7\text{BrN}_2\text{O}$: 213.97, found: 214.0; Anal. Calc. for $\text{C}_7\text{H}_7\text{BrN}_2\text{O}$: C, 39.09; H, 3.28; N, 13.03. Found: C, 39.40; H, 3.57; N, 12.88.

2-Amino-5-iodobenzamide (3e). White solid (0.232 g, 89%); mp 177-178 °C; IR ν_{\max} (KBr) 3395.1, 3287.1, 3172.3, 1674.9 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.85 (br s, 1H), 7.81 (d, J 1.5 Hz, 1H), 7.38 (dd, J 9.0, 2.0 Hz, 1H), 7.16 (br s, 1H), 6.70 (br s, 2H), 6.55 (d, J 8.5 Hz, 1H); ^{13}C NMR δ 171.4, 151.1, 141.2, 137.8, 120.2, 117.3, 75.4; MS (EI): m/z [M^+] calcd. for $\text{C}_7\text{H}_7\text{IN}_2\text{O}$: 261.95, found: 262.0; Anal. Calc. for $\text{C}_7\text{H}_7\text{IN}_2\text{O}$: C, 32.08; H, 2.69; N, 10.69. Found: C, 32.45; H, 3.01; N, 10.36.

2-Amino-4,5-dimethoxybenzamide (3f). White solid (0.160 g, 82%); mp 148-149 °C; IR ν_{\max} (KBr) 3438.5, 3337.2, 3238.0 cm^{-1} , 1681.6; ^1H NMR (DMSO- d_6) δ 7.58 (br s, 1H), 7.12 – 7.09 (m, 1H), 6.82 (br s, 1H), 6.44 (br s, 2H), 6.30 – 6.26 (m, 1H), 3.72 (s, 3H), 3.67 (s, 3H); ^{13}C NMR δ 172.4, 154.3, 148.1, 140.2, 114.1, 105.3, 100.8, 57.4, 55.9; MS (EI): m/z [M^+] calcd. for

C₉H₁₂N₂O₃: 196.08, found: 196.0; Anal. Calc. for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.28; H, 6.54; N, 13.92.

2-Amino-3,5-dibromobenzamide (3g). White solid (0.250 g, 85%); mp 214-215 °C; IR ν_{\max} (KBr) 3366.1, 3322.7, 3179.1, 1652.7 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.06 (br s, 1H), 7.79 – 7.76 (m, 1H), 7.74 – 7.72 (m, 1H), 7.47 (br s, 1H), 6.80 (br s, 2H); ¹³C NMR δ 170.7, 147.3, 137.9, 131.9, 118.0, 111.5, 106.0; MS (EI): *m/z* [M⁺] calcd. for C₇H₆ Br₂N₂O: 291.88, found: 291.9; Anal. Calc. for C₇H₆ Br₂N₂O: C, 28.60; H, 2.06; N, 9.53. Found: C, 28.85; H, 2.43; N, 9.23.

General experimental procedure for the preparation of secondary (4a-i) and tertiary athranilamides (5a-h). *N*-(2-Aminoarylacyl)benzotriazoles (1 mmol) and various primary and secondary amines (1.2 mmol) were left to stir in CH₂Cl₂ (10 mL) for 2-6 hours at room temperature. After the reaction ended, the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel with EtOAc/ *n*-hexane prepared in different proportions to afford secondary and tertiary amides.

2-Amino-*N*-benzylbenzamide (4a). White solid (0.160 g, 71%); mp 121-122 °C; IR ν_{\max} (KBr) 3467.4, 3359.4, 3301.5, 1638.2 cm⁻¹; ¹H NMR (CDCl₃) δ 7.41 – 7.38 (m, 4H), 7.36 – 7.33 (m, 2H), 7.26 – 7.22 (m, 1H), 6.72 (d, *J* 8.2 Hz, 1H), 6.66 (t, *J* 7.5 Hz, 1H), 6.35 (br s, 1H), 5.62 (br s, 2H), 4.64 (d, *J* 5.6 Hz, 2H); ¹³C NMR δ 169.2, 148.8, 138.3, 132.4, 128.8, 127.8, 127.6, 127.1, 117.4, 116.7, 115.9, 43.8; MS (EI): *m/z* [M⁺] calcd. for C₁₄H₁₄N₂O: 226.11, found: 226.1; Anal. Calc. for C₁₄H₁₄N₂O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.02; H, 6.37; N, 12.09.

2-Amino-3-methyl-*N*-propylbenzamide (4b). White solid (0.152 g, 79%); mp 105-106 °C; IR ν_{\max} (KBr) 3424.0, 3301.5, 1623.8 cm⁻¹; ¹H NMR (CDCl₃) δ 7.23 (d, *J* 7.8 Hz, 1H), 7.15 (d, *J* 7.3 Hz, 1H), 6.62 (t, *J* 7.6 Hz, 1H), 6.10 (br s, 1H), 5.63 (br s, 2H), 3.40 (q, *J* 6.7 Hz, 2H), 2.19 (s, 3H), 1.65 (sex, *J* 7.3 Hz, 2H), 1.01 (t, *J* 7.4 Hz, 3H); ¹³C NMR δ 170.9, 147.7, 133.8, 125.6, 124.6, 116.8, 41.7, 23.1, 17.6, 11.6; MS (EI): *m/z* [M⁺] calcd. for C₁₁H₁₆N₂O: 192.12, found: 192.1; Anal. Calc. for C₁₁H₁₆N₂O: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.68; H, 8.36; N, 14.36.

2-Amino-*N*-cyclohexyl-4-methylbenzamide (4c). White solid (0.200 g, 86%); mp 150-151 °C; IR ν_{\max} (KBr) 3474.1, 3359.4, 3301.5, 1638.2 cm⁻¹; ¹H NMR (CDCl₃) δ 7.20 (d, *J* 8.0 Hz, 1H), 6.52 (s, 1H), 6.49 (d, *J* 8.0 Hz, 1H), 5.89 (d, *J* 6.5 Hz, 1H), 5.57 (br s, 2H), 3.97 – 3.91 (m, 1H), 2.25 (s, 3H), 2.05 – 2.01 (m, 2H), 1.79 – 1.75 (m, 2H), 1.69 – 1.65 (m, 1H), 1.48 – 1.40 (m, 2H), 1.20 – 1.28 (m, 3H); ¹³C NMR δ 168.4, 148.6, 142.6, 126.9, 117.9, 117.7, 114.0, 48.2, 33.3, 25.6, 24.9, 21.4; MS (EI): *m/z* [M⁺] calcd. for C₁₄H₂₀N₂O: 232.15, found: 232.1; Anal. Calc. for C₁₄H₂₀N₂O: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.01; H, 8.69; N, 11.86.

2-Amino-*N*-cyclohexyl-5-methylbenzamide (4d). White solid (0.200 g, 86%); mp 201-202 °C; IR ν_{\max} (KBr) 3417.2, 3294.8, 1631.5 cm⁻¹; ¹H NMR (CDCl₃) δ 7.11 (s, 1H), 7.06 (d, *J* 8.8 Hz, 1H), 6.68 (d, *J* 8.5 Hz, 1H), 5.96 (br s, 1H), 5.40 (br s, 2H), 3.95 – 3.93 (m, 1H), 2.29 – 2.24 (m, 2H), 2.05 – 2.02 (m, 2H), 1.79 – 1.76 (m, 2H), 1.69 – 1.66 (m, 1H), 1.46 – 1.41 (m, 2H), 1.30 – 1.22 (m, 4H); ¹³C NMR δ 169.4, 146.2, 133.7, 127.9, 127.2, 118.6, 118.0, 48.6, 33.5, 25.8, 25.1,

20.6; MS (EI): m/z [M^+] calcd. for $C_{14}H_{20}N_2O$: 232.15, found: 232.1; Anal. Calc. for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.15; H, 8.85; N, 11.84.

2-Amino-5-methoxy-*N*-propylbenzamide (4e). White solid (0.171 g, 82%); mp 72-74 °C; IR ν_{max} (KBr) 3413.4, 3301.5, 1654.6 cm^{-1} ; 1H NMR ($CDCl_3$) δ 6.90 – 6.87 (m, 2H), 6.68 (d, J 8.5 Hz, 1H), 6.22 (br s, 1H), 5.01 (br s, 2H), 3.77 (s, 3H), 3.38 (q, J 6.7 Hz, 2H), 1.64 (sex, J 7.2 Hz, 2H), 0.99 (t, J 7.5 Hz, 3H); ^{13}C NMR δ 169.0, 151.3, 142.0, 118.8, 118.7, 118.1, 112.3, 56.1, 41.5, 23.0, 11.5; MS (EI): m/z [M^+] calcd. for $C_{11}H_{16}N_2O_2$: 208.12, found: 208.1; Anal. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.48; H, 7.86; N, 13.74.

2-Amino-4-chloro-*N*-methylbenzamide (4f). White solid (0.172 g, 93%); mp 96-97 °C; IR ν_{max} (KBr) 3467.4, 3366.1, 3337.2, 1638.2 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.24 (d, J 8.4 Hz, 1H), 6.69 (d, J 2.0 Hz, 1H), 6.60 (dd, J 8.4, 2.0 Hz, 1H), 6.19 (br s, 1H), 5.66 (br s, 2H), 2.96 (d, J 5.2 Hz, 3H); ^{13}C NMR δ 169.3, 149.7, 137.9, 128.4, 116.6, 116.5, 114.5, 26.6; MS (EI): m/z [M^+] calcd. for $C_8H_9ClN_2O$: 184.03, found: 184.0; Anal. Calc. for $C_8H_9ClN_2O$: C, 52.03; H, 4.91; N, 15.17. Found: C, 52.34; H, 5.22; N, 14.86.

2-Amino-5-bromo-*N*-isopropylbenzamide (4g). White solid (0.224 g, 87%); mp 188-189 °C; IR ν_{max} (KBr) 3467.4, 3366.1, 3287.1, 1631.5 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.40 (d, J 2.2 Hz, 1H), 7.29 (dd, J 8.5, 2.4 Hz, 1H), 6.59 (d, J 8.7 Hz, 1H), 5.82 (br s, 1H), 5.53 (br s, 2H), 4.24 (sep, J 6.6 Hz, 1H), 1.28 (d, J 6.6 Hz, 6H); ^{13}C NMR δ 168.3, 148.5, 135.5, 130.3, 119.6, 118.8, 108.3, 42.0, 23.0; MS (EI): m/z [M^+] calcd. for $C_{10}H_{13}BrN_2O$: 256.02, found: 256.0; Anal. Calc. for $C_{10}H_{13}BrN_2O$: C, 46.71; H, 5.10; N, 10.89. Found: C, 46.69; H, 5.43; N, 10.55.

2-Amino-3,5-dichloro-*N*-propylbenzamide (4h). White solid (0.234 g, 95%); mp 143-144 °C; IR ν_{max} (KBr) 3430.7, 3287.1, 1638.2 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.36 (d, J 2.3 Hz, 1H), 7.24 (d, J 2.3 Hz, 1H), 6.06 (br s, 1H), 5.98 (br s, 2H), 3.39 (q, J 6.7 Hz, 2H), 1.66 (sex, J 7.3 Hz, 2H), 1.01 (t, J 7.4 Hz, 3H); ^{13}C NMR δ 168.6, 144.5, 132.3, 126.1, 122.0, 120.8, 118.8, 41.9, 23.0, 11.5; MS (EI): m/z [M^+] calcd. for $C_{10}H_{12}Cl_2N_2O$: 246.03, found: 246.0; Anal. Calc. for $C_{10}H_{12}Cl_2N_2O$: C, 48.58; H, 4.89; N, 11.33. Found: C, 48.82; H, 5.23; N, 11.07.

2-Amino-4,5-dimethoxy-*N*-methylbenzamide (4i). White solid (0.176 g, 84%); mp 117-119 °C; IR ν_{max} (KBr) 3455.8, 3390.2, 3336.2, 1631.5 cm^{-1} ; 1H NMR ($CDCl_3$) δ 6.84 (s, 1H), 6.20 (s, 1H), 6.19 (br s, 1H), 5.40 (br s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.94 (d, J 4.5 Hz, 3H); ^{13}C NMR δ 169.7, 153.1, 144.6, 140.8, 110.9, 107.3, 100.8, 56.9, 55.7, 26.5; MS (EI): m/z [M^+] calcd. for $C_{10}H_{14}N_2O_3$: 210.09, found: 210.1; Anal. Calc. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.08; H, 6.66; N, 13.61.

(2-Aminophenyl)(piperidin-1-yl)methanone (5a). White solid (0.184 g, 90%); mp 74-76 °C; IR ν_{max} (KBr) 3488.5, 3359.4, 3251.4, 1652.7 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.15 (t, J 7.7 Hz, 1H), 7.07 (dd, J 7.5, 1.5 Hz, 1H), 6.72 – 6.69 (m, 2H), 4.28 (s, 2H), 3.55 (br s, 4H), 1.68 – 1.60 (m, 6H); ^{13}C NMR δ 169.7, 145.4, 130.3, 127.6, 120.5, 117.4, 116.6, 26.4, 26.2, 24.6; MS (EI): m/z [M^+] calcd. for $C_{12}H_{16}N_2O$: 204.12, found: 204.1; Anal. Calc. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 76.56; H, 8.22; N, 13.77.

(2-Amino-3-methylphenyl)(piperidin-1-yl)methanone (5b). White solid (0.188 g, 86%); mp 80-81 °C; IR ν_{max} (KBr) 3430.7, 3351.7, 1617.0 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.05 (s, J 7.5 Hz, 1H),

6.95 (s, *J* 7.5 Hz, 1H), 6.64 (t, *J* 7.5 Hz, 1H), 4.25 (s, 2H), 3.55 (br s, 4H), 2.17 (s, 3H), 1.67 – 1.59 (m, 6H); ¹³C NMR δ 170.1, 143.5, 131.2, 125.4, 123.3, 120.0, 117.0, 26.2, 26.1, 24.6, 17.5; MS (EI): *m/z* [*M*⁺] calcd. for C₁₃H₁₈N₂O: 218.14, found: 218.1; Anal. Calc. for C₁₃H₁₈N₂O: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.19; H, 8.31; N, 13.20.

(2-Amino-6-methylphenyl)(pyrrolidin-1-yl)methanone (5c). White solid (0.192 g, 94%); mp 78-79 °C; IR ν_{max} (KBr) 3430.8, 3330.5, 3229.2, 1617.0 cm⁻¹; ¹H NMR (CDCl₃) δ 7.05 (t, *J* 7.8 Hz, 1H), 6.63 (d, *J* 7.5 Hz, 1H), 6.56 (d, *J* 8.0 Hz, 1H), 3.79 (br s, 2H), 3.73 – 3.64 (m, 2H), 3.28 – 3.23 (m, 1H), 3.19 – 3.14 (m, 1H), 2.24 (s, 3H), 2.02 – 1.88 (m, 4H); ¹³C NMR δ 170.0, 143.4, 135.1, 130.0, 125.4, 121.0, 114.2, 47.6, 45.5, 26.1, 24.8, 19.1; MS (EI): *m/z* [*M*⁺] calcd. for C₁₂H₁₆N₂O: 204.12, found: 204.0; Anal. Calc. for C₁₂H₁₆N₂O: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.92; H, 8.17; N, 13.67.

(2-Amino-5-chlorophenyl) (morpholino) methanone (5d). Pale yellow solid (0.216 g, 90%); mp 130-131 °C; IR ν_{max} (KBr) 3424.0, 3337.2, 3236.9, 1617.0 cm⁻¹; ¹H NMR (CDCl₃) δ 7.14 (dd, *J* 8.6, 2.3 Hz, 1H), 7.05 (d, *J* 2.3 Hz, 1H), 6.67 (d, *J* 8.6 Hz, 1H), 4.35 (br s, 2H), 3.72 – 3.64 (m, 8H); ¹³C NMR δ 169.6, 145.2, 131.5, 128.2, 122.9, 121.0, 118.7, 67.4 (2C); MS (EI): *m/z* [*M*⁺] calcd. for C₁₁H₁₃ClN₂O₂: 240.06, found: 240.0; Anal. Calc. for C₁₁H₁₃ClN₂O₂: C, 54.88; H, 5.83; N, 11.64. Found: C, 54.89; H, 6.01; N, 11.34.

(2-Amino-5-iodophenyl)(pyrrolidin-1-yl)methanone (5e). Brown solid (0.280 g, 89%); mp 134-135 °C; IR ν_{max} (KBr) 3417.2, 3322.7, 3208.0, 1645.9 cm⁻¹; ¹H NMR (CDCl₃) δ 7.49 (d, *J* 2.5 Hz, 1H), 7.42 (dd, *J* 8.5, 2.0 Hz, 1H), 6.52 (d, *J* 8.5 Hz, 1H), 4.58 (br s, 2H), 3.63 (s, 2H), 3.49 (s, 2H), 1.97 (s, 2H), 1.92 (s, 2H); ¹³C NMR δ 167.8, 145.6, 139.1, 136.2, 122.9, 118.8, 49.6, 46.1, 26.4, 24.4; MS (EI): *m/z* [*M*⁺] calcd. for C₁₁H₁₃IN₂O: 316.00, found: 315.9; Anal. Calc. for C₁₁H₁₃IN₂O: C, 41.79; H, 4.15; N, 8.86. Found: C, 42.07; H, 4.61; N, 8.60.

2-Amino-3,5-dibromo-*N,N*-diethylbenzamide (5f). Colourless oil (0.312 g, 89%); IR ν_{max} (KBr) 3452.9, 3344.9, 1617.0 cm⁻¹; ¹H NMR (CDCl₃) δ 7.53 (d, *J* 2.2 Hz, 1H), 7.13 (d, *J* 2.2 Hz, 1H), 4.62 (s, 2H), 3.41 (br s, 4H), 1.17 (br s, 6H); ¹³C NMR δ 168.2, 141.7, 135.1, 128.6, 123.6, 111.0, 108.5, 43.4, 39.8, 39.5, 13.5; MS (EI): *m/z* [*M*⁺] calcd. for C₁₁H₁₄Br₂N₂O: 347.94, found: 348.0; Anal. Calc. for C₁₁H₁₄Br₂N₂O: C, 37.74; H, 4.03; N, 8.00. Found: C, 37.69; H, 4.44; N, 7.85.

(2-Amino-3,5-diiodophenyl) (morpholino) methanone (5g). White solid (0.440 g, 96%); mp 128-130 °C; IR ν_{max} (KBr) 3467.4, 3378.7, 3336.2, 1631.5 cm⁻¹; ¹H NMR (CDCl₃) δ 7.95 (d, *J* 1.0 Hz, 1H), 7.32 (d, *J* 1.5 Hz, 1H), 4.84 (br s, 2H), 3.71 – 3.63 (m, 8H); ¹³C NMR δ 167.5, 147.3, 145.3, 136.0, 120.8, 87.1, 77.7, 66.9, 31.0; MS (EI): *m/z* [*M*⁺] calcd. for C₁₁H₁₂I₂N₂O₂: 457.89, found: 457.9; Anal. Calc. for C₁₁H₁₂I₂N₂O₂: C, 28.84; H, 2.64; N, 6.12. Found: C, 29.03; H, 2.86; N, 6.45.

2-Amino-*N,N*-diethyl-3,4,5-trimethoxybenzamide (5h). Dark yellow oil (0.262 g, 93%); IR ν_{max} (KBr) 3452.9, 3351.7, 1631.5 cm⁻¹; ¹H NMR (CDCl₃) δ 6.48 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.45 (br s, 6H), 1.23 (s, 6H); ¹³C NMR δ 170.2, 145.2, 143.7, 141.9, 133.1, 116.5, 106.3, 60.9, 60.5, 56.7, 13.6; MS (EI): *m/z* [*M*⁺] calcd. for C₁₄H₂₂N₂O₄: 282.15, found:

282.1; Anal. Calc. for C₁₄H₂₂N₂O₄: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.19; H, 7.51; N, 10.29.

Acknowledgements

This work is dedicated to Professor Cemil Öğretir, who died on 19th January, 2011. It is gratefully acknowledged that this work was supported financially by Anadolu University (Project No: 1002F88) and we are also grateful to AUBIBAM for providing ¹H and ¹³C NMR spectra.

References

1. Bettelheim, F. A.; March, J. *Introduction to General, Organic and Biochemistry*, 5th Ed.; Sounders College Publishing: Fort Worth, 1998; pp 492–508.
2. Chung, Y. J.; Jung, Y. S.; Seong, C. M.; Park, N. S. *Bull. Korean Chem. Soc.* **1998**, *19* (10), 1117.
3. (a) Siddiqui, I. R.; Siddique, S. A.; Srivastava, V.; Singh, P. K.; Singh, J. *Arkivoc* **2008**, (xii), 277. (b) Subba Reddy, B. V.; Venkateswarlu, A.; Madan, C.; Vinu, A. *Tetrahedron Lett.* **2011**, *52*, 1891. (c) Loseva, M. V.; Bolotin, B. M. *Chemistry of Heterocyclic Compounds* **1972**, *10*, 1212.
4. Shariat, M.; Abdollahi, S. *Molecules* **2004**, *9*, 705.
5. Nishimura, T.; Iino, T.; Mitsuya, M.; Bamba, M.; Watanabe, H.; Tsukahara, D.; Kamata, K.; Sasaki, K.; Ohyama, S.; Hosaka, H.; Futamura, M.; Nagata, Y.; Eiki, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1357.
6. Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 883.
7. (a) Tani, J.; Yamada, Y.; Oine, T.; Ochiai, T.; Ishida, R.; Inoue, I. *J. Med. Chem.* **1979**, *22*, 95. (b) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129. (c) Wright, W. B.; Tomcufcik, A. S.; Chan, P. S.; Marsico, J. W.; Press, J. B. *J. Med. Chem.* **1987**, *30*, 2277. (d) Lee, J. S.; Oh, Y. S.; Lim, J. K.; Yang, W. Y.; Kim, I. H.; Lee, C. W.; Chung, Y. H.; Yoon, S. J. *Synth. Commun.* **1999**, *29*, 2547. (e) Larsen, U. S.; Begtrup, M.; Martiny, L. *J. Label. Compd. Radiopharm.* **2005**, *48*, 429. (f) Asano, T.; Yoshikawa, T.; Usui, T.; Yamamoto, H.; Yamamoto, Y.; Uehara, Y.; Nakamura, H. *Bioorg. Med. Chem.* **2004**, *12*, 3529.
8. Rivière-Baudet, M.; Morère, A.; Dias, M. *Tetrahedron Lett.* **1992**, *33*, 6453.
9. Sellstedt, J. H.; Guinasso, C. J.; Begany, A. J.; Bell, S. C.; Rosenthale, M. *J. Med. Chem.* **1975**, *18*, 926.

10. Asano, T.; Yoshikawa, T.; Nakamura, H.; Ueharac, Y.; Yamamoto, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2299.
11. Staiger, R. P.; Miller, E. B. *J. Org. Chem.* **1959**, *24*, 1214.
12. Allison, B. D.; Phuong, V. K.; McAtee, L. C.; Rosen, M.; Morton, M.; Prendergast, C.; Barrett, T.; Lagaud, G.; Freedman, J.; Li, L.; Wu, X.; Venkatesan, H.; Pippel, M.; Woods, C.; Rizzolio, M. C.; Hack, M.; Hoey, K.; Deng, X.; King, C.; Shankley, N. P.; Rabinowitz, M. H. *J. Med. Chem.* **2006**, *49*, 6371.
13. (a) Katritzky, A. R.; Mohapatra, P. P.; Huang, L. *Arkivoc* **2008**, (ix), 62. (b) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811.
14. (a) Katritzky, A. R.; He, H-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, *11*, 1656. (c) Celik, İ.; Abdel-Fattah, A. A. *Tetrahedron* **2009**, *65*, 4923.
15. (a) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *CCACAA* **2004**, *77* (1–2), 175. (b) Wang, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 5431.
16. (a) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *Synthesis* **2004**, *11*, 1806. (b) Lin, S-M.; Zhang, J-L.; Chen, J-K.; Gao, W-X.; Ding, J-C.; Su, W-K.; Wu, H-Y. *J. Braz. Chem. Soc.* **2010**, *21*, 1616.
17. Katritzky, A. R.; Singh, S. K.; Cai, C.; Bobrov, S. *J. Org. Chem.* **2006**, *71* (9), 3364.
18. Katritzky, A. R.; Meher, N. K.; Cai, C.; Singh, S. K. *Rev. Soc. Quím. Méx.* **2004**, *48*, 275.
19. Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, *18*, 2795.
20. Katritzky, A. R.; Vakulenko, A. V.; Jain, R. *Arkivoc* **2003**, (xiv), 131.
21. (a) Zhao, H.; Fu, H.; Qiao, R. *J. Org. Chem.* **2010**, *75*, 3311. (b) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.
22. Staiger, R. P.; Wagner, E. C. *J. Org. Chem.* **1948**, *13*, 347.
23. Javier, B. O.; Manuel, A. L. PCT Int. Appl., 2001 066 519, 2001.
24. Varasi, M.; Thaler, F.; Abate, A.; Carenzi, G.; Minucci, S. PCT Int. Appl., 2009 127 609, 2009.
25. Sardon, T.; Cottin, T.; Xu, J.; Giannis, A.; Vernos, I. *ChemBioChem* **2009**, *10*, 464.
26. Wong, N. C. W.; Tucker, J. E. L.; Hansen, H. C.; Chiacchia, F. S.; McCaffrey, D. U.S. Pat. Appl. Publ., 2008 0188 467, 2008.
27. Eger, K. *Arch. Pharm.* **1981**, *314*, 176.
28. Petrov, J. S.; Andreev, G. N. *Org. Prep. Proced. Int.* **2005**, *37*, 560.
29. Kornet, M. J. *J. Heterocycl. Chem.* **1992**, *29*, 103.
30. Barlaam, B. C.; Foote, K. M.; Ple, P. PCT Int. Appl., 2009153589, 2009.
31. Ogita, H.; Isobe, Y.; Takaku, H.; Sekine, R.; Goto, Y.; Misawa, S.; Hayashi, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 549.