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Journal of Fluorine Chemistry 126 (2005) 759–763
JOURNAL OF FLUORINE CHEMISTRY
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Synthesis and biological activity of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles☆

Anton V. Dolzhenko [a], Wai-Keung Chui [a,*], Anna V. Dolzhenko [b], Lai-Wah Chan [a]

[a] *Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore*
[b] *Perm State Pharmaceutical Academy, 48 Lenin Street, Perm 614990, Russian Federation*

Received 27 December 2004; received in revised form 14 February 2005; accepted 17 February 2005
Available online 13 April 2005

Abstract

The heterocyclic nucleus *s*-triazino[1,2-*a*]benzimidazole has been reported to exhibit antibacterial activity. In this study, seven new 3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazole derivatives were prepared via cyclocondensation between 2-guanidinobenzimidazole and fluorine substituted (including trifluoromethyl) benzaldehydes. The structures of all the compounds were confirmed by ^{1}H, ^{13}C NMR and IR spectral data. Spectral data also suggested the existence of various tautomeric forms of the fluorine-containing *s*-triazino[1,2-*a*]benzimidazole compounds. The synthesized compounds were also screened for antibacterial and bovine dihydrofolate reductase (DHFR) inhibitory activities. The compound **3g** substituted with a 3′,5′-bis(trifluoromethyl)phenyl moiety demonstrated the best antibacterial activity in the series. None of the tested compounds significantly inhibited bovine DHFR.

Keywords: 2-Guanidinobenzimidazole; Cyclocondensation; *s*-Triazino[1,2-a]benzimidazole; Antibacterial activity; Dihydrofolate reductase inhibition

1. Introduction

A variety of biological effects have been attributed to the heterocyclic nucleus *s*-triazino[1,2-*a*]benzimidazole [2–14]. In particular, 2-amino-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles have been found to possess both antibacterial [2] and dihydrofolate reductase (DHFR) inhibitory [3,4] activities.

The synthesis of 2-amino-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles through a base catalyzed cyclization of 2-guanidinobenzimidazole (**2**) with benzaldehyde was first reported by Nagarajan et al. in 1970 [15]. To date only a limited number of studies on the synthesis of the above mentioned 2-amino-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles have been reported [1,2,16,17]. Fluorinated compound **3c** has been reported to be synthesized; however no spectral data and elemental analysis results were presented in the article [2]. Our laboratory has been working on the *s*-triazine DHFR inhibitors for sometime [18], it is therefore of interest to us to explore the modification of the *s*-triazino[1,2-*a*]benzimidazole nucleus in an attempt to search for new potential inhibitors of DHFR. The objective of this study was to introduce an aryl group at position 4 of the heterocycle through condensation of the guanidino intermediate with benzaldehydes. Fluorinated (including trifluoromethyl) benzaldehydes were used in the synthesis for the purpose of investigating whether fluorinated aryl group attached to the heterocyclic nucleus will give rise to DHFR inhibitory and antibacterial activity. In our laboratory, it was found that lipophilic groups attached to the dihydro-*s*-triazines appeared to give better DHFR inhibitory activity. Therefore, for this study we intended to investigate if lipophilic fluorinated derivatives of 2-amino-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles would exhibit DHFR inhibitory activity.

☆ Part 2 in the series 'Fused heterocyclic systems with *s*-triazine ring' [1]

* Corresponding author. Tel.: +65 6874 2933; fax: +65 6779 1554.
E-mail address: phacwk@nus.edu.sg (W.-K. Chui).

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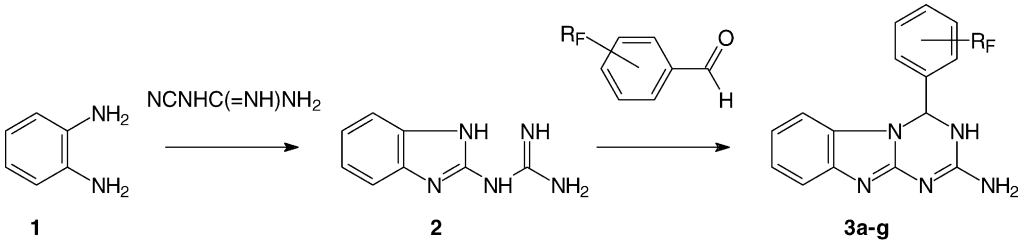
doi:10.1016/j.jfluchem.2005.02.009



1 2 3a-g

	R_F
3a	2-F
3b	3-F
3c	4-F
3d	2-CF_3
3e	3-CF_3
3f	4-CF_3
3g	3,5-$(CF_3)_2$

Scheme 1. The synthesis of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles (**3a–g**).

2. Results and discussion

2.1. Chemistry

2-Guanidinobenzimidazole (**2**) was prepared by the cyclocondensation of *o*-phenylenediamine (**1**) with cyanoguanidine according to the method reported by King et al. [19]. The piperidine-catalyzed reaction of **2** with fluorinated aromatic aldehyde in refluxing ethanol, led to a cyclization process with the formation of an *s*-triazine ring (Scheme 1). This chemical reaction proceeded smoothly and the yields of the products were generally good, ranging from 64 to 90%.

The structures of the synthesized 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles (**3a–g**) were elucidated with the help of IR and NMR spectral data as well as elemental analyses. The presence of the 2-NH_2 group in the structure was supported with a significant stretching absorption signal (ν_{N-H}) observed at 3224–3474 cm^{-1} and the scissoring absorption signal (δ_{N-H}) appearing at 1605–1625 cm^{-1} in the IR spectra of compounds **3a–g**.

The assignment of ^1H and ^{13}C NMR signals was made based on the data for analogous compounds [1,16,20] and the electronic effect of the substituents. The formation of the *s*-triazine ring in the reaction was suggested by the NMR spectral data (Table 1). The singlet of H-4 observed at 6.80–7.06 ppm in the ^1H NMR spectra of **3a–g**, together with the signal of C-4 at 61.2–65.1 ppm in the ^{13}C NMR spectra confirmed the formation of the dihydro-*s*-triazine ring. This strong evidence of the sp^3 hybridization of C-4 ruled out the possible formation of the azomethine carbon of Schiff base-like compounds. At the same time, the signals of the other two carbon atoms of the *s*-triazine ring (C-2 and C-10a), surrounded by three nitrogen atoms each, were found located at 154.9–155.2 and 153.1–153.7 ppm, respectively. This provided further evidence for the formation of the triazine ring.

It should be noted that the compounds **3a–g** could exist in three tautomeric forms, namely, 3,4-dihydro- (**A**), 1,4-dihydro- (**B**) and 4,10-dihydro- (**C**) (Fig. 1). The prototropic interconversion between these tautomeric forms was postulated based on the broadening of the signals of dihydro[1,3,5]-triazino[1,2-*a*]benzimidazole heterocyclic system in the ^{13}C NMR spectra of the compounds **3a–g**, particularly, the signals of C-2, C-4, C-10a that are in close proximity with the nitrogen atoms that are involved in the tautomerization. However, in compound **3c** a broad signal in the ^{13}C NMR spectrum was observed for C-9a. This observation, together with a large broadening effect of the NH signal in ^1H NMR spectrum of this compound **3c**, might indicate the predominant existence of the 1,4-dihydro- and the 4,10-dihydro- tautomeric forms (**B** and **C**) during the equilibrium state.

Table 1
^1H and ^{13}C NMR spectral data for the *s*-triazine ring of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles (**3a–g**)

Compound	R_F	^1H NMR, δ (ppm)		^{13}C NMR, δ (ppm)		
		H-4	NH	C-2	C-4	C-10a
3a	2-F	7.06	8.30	155.2	61.2	153.3
3b	3-F	6.80	8.09	155.3	64.9	153.3
3c	4-F	6.82	8.25	155.2	65.1	153.2
3d	2-CF_3	7.01	7.90	154.9	62.1	153.7
3e	3-CF_3	6.97	8.36	155.2	64.9	153.3
3f	4-CF_3	6.97	8.51	155.3	65.0	153.3
3g	3,5-$(CF_3)_2$	7.06	8.26	155.1	64.2	153.1

2.2. Biological activity

For both the antibacterial and DHFR inhibition bioassays, the compounds were dissolved in Me_2SO. In order to ensure that the solvent per se had no effect on bacterial growth or enzymatic activity, negative control tests were performed using Me_2SO at the same concentrations.

In the antibacterial bioassay, the minimum inhibitory concentrations (MIC) were determined using the two-fold

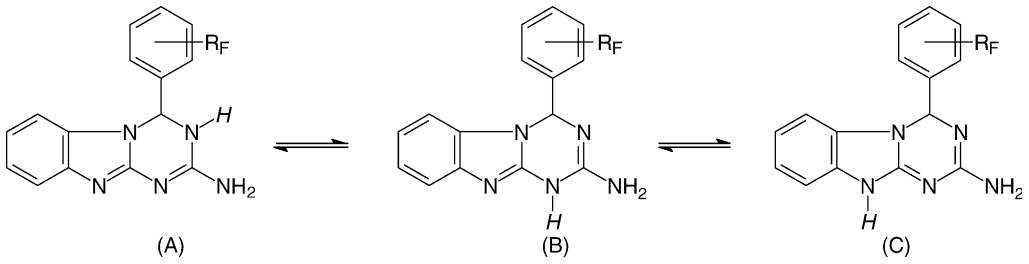


Fig. 1. The tautomeric forms of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles (**3a–g**).

Table 2
Biological activity of the fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles (**3a-g**)

Compound	R_F	Antibacterial effect, MIC (μg ml^{-1})					Bovine DHFR inhibition	
		S. aureus	*B. subtilis*	*B. megaterium*	*K. aerogenes*	*E. coli*	Concentration (mM)	Inhibition (%)
3a	2-F	>200	>200	>200	>200	>200	0.5	3
3b	3-F	>200	>200	>200	>200	>200	1	7
3c	4-F	100	>200	>200	>200	>200	1	15.5
3d	2-CF_3	100	>100	>100	>100	>100	0.2	11
3e	3-CF_3	>25	>25	>25	>25	>25	–	ND[a]
3f	4-CF_3	>25	>25	>25	>25	>25	0.1	6
3g	3,5-$(CF_3)_2$	25	25	>25	>25	>25	–	ND[a]
Tetracycline	–	0.63	0.63	0.63	1.25	1.25	–	–

[a] ND: not determined due to solubility problems.

serial dilution technique [21]. The following bacteria were used for screening: *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus megaterium*, *Klebsiella aerogenes*, and *Escherichia coli*. The compounds did not inhibit the growth of the bacteria *B. megaterium*, *K. aerogenes*, and *E. coli* at the concentrations used. However, three of the *s*-triazino[1,2-*a*]benzimidazoles (**3c**,**d** and **g**) did exhibit weak antibacterial effect against *S. aureus* and *B. subtilis* in comparison to the reference drug tetracycline (Table 2). The most active compound in the series was found to be compound **3g** which possesses the 3′,5′-bis(trifluoromethyl)phenyl moiety.

The DHFR inhibition bioassay was carried out using bovine DHFR (Fluka Chemie) according to the previously described method [18], the effect of the compounds was expressed as percentage inhibition (Table 2). The compounds were screened at one of the following concentrations 0.1, 0.2, 0.5 and 1.0 mM depending on solubility. Because of the poor solubility of the 3′-trifluoromethyl substituted derivatives (**3e**,**g**) in the bioassay medium, they could not be tested in these concentrations. The screening found that none of the *s*-triazino[1,2-*a*]benzimidazoles showed significant inhibition of bovine DHFR.

3. Conclusions

The present work has demonstrated the use of a simple cyclocondensation method for the synthesis of fluorinated 2-amino-4-aryl-3,4-dihydro[1,3,5]triazine[1,2-*a*]benzimidazoles. This method was able to give reasonably good and clean yields. Seven derivatives were prepared and biologically evaluated for both antibacterial and DHFR inhibitory activities. The basic 2-NH_2 group and its adjacent N atom are believed to interact with specific amino acids at the active site of the DHFR enzyme. However, the 4-aryl substituent may be too large for the compound to fit properly in the active site; hence a lack of DHFR inhibitory was observed. Nevertheless, three of the compounds (**3c**,**d** and **g**) were found to possess some degree of antimicrobial activity. Therefore they may be used as lead compounds for further development.

4. Experimental

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using Me_2SO-d_6 as a solvent and TMS as an internal reference. IR spectra were performed on a Jasco FT-IR-430 spectrophotometer in KBr pellets. The course of the reactions was monitored by TLC on Silica gel 60 F_{254} plates (Merck, Germany). 2-Guanidinobenzimidazole (**2**) was prepared using reported method [19].

4.1. General method for the syntheses of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazoles (3a–g)

A solution of 2-guanidinobenzimidazole (**2**, 1.75 g, 0.01 mol), fluorine or trifluoromethyl substituted benzaldehyde (0.01 mol) and 0.5 ml piperidine in ethanol (20–50 ml)

was heated under reflux for 1–8 h (vide infra). After cooling, the product was filtered, washed with ethanol and dried.

4.2. 2-Amino-4-(2′-fluorophenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3a**)

Reaction time 1.5 h; yield 90%; mp 276–277 °C; IR (KBr): ν 3474 (NH st), 3323 (NH st), 3251 (NH st), 3109 (CH st), 2968 (CH st), 2757 (CH st), 1659 (C=N st), 1625 (NH δ), 1590, 1531, 1457, 1433, 1405, 1276, 1252, 1224, 769, 734, 706 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.65 (2H, *s*, NH_2), 6.75 (1H, *d*, *J* = 7.2 Hz, H-9), 6.81 (1H, *t*, *J* = 7.3 Hz, H-8), 6.95 (1H, *t*, *J* = 7.7 Hz, H-7), 7.05 (1H, *s*, H-4), 7.15–7.26 (3H, *m*, H-3′, H-5′ and H-6′), 7.27 (1H, *d*, *J* = 8.4 Hz, H-6), 7.41 (1H, *td*, *J* = 7.6 Hz, J_{HF} = 5.3 Hz, H-4′), 8.30 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 61.2 (*s*, C-4), 107.5 (*s*, C-6), 115.9 (*s*, C-9), 116.0 (*d*, *J* = 19.6 Hz, C-3′), 119.0 (*s*, C-8), 120.9 (*s*, C-7), 124.9 (*d*, *J* = 3.6 Hz, C-6′), 126.9 (*d*, *J* = 10.2 Hz, C-4′), 128.1 (*d*, *J* = 2.9 Hz, C-5′), 131.0 (*s*, C-5a), 131.3 (*d*, *J* = 8.0 Hz, C-1′), 143.2 (*s*, C-9a), 153.3 (*s*, C-10a), 155.2 (*s*, C-2), 159.5 (*d*, *J* = 247.8 Hz, C-2′). Anal. Calcd. for $C_{15}H_{12}FN_5$: C, 64.05; H, 4.30; N, 24.90. Found: C, 63.86; H, 4.22; N, 24.56.

4.3. 2-Amino-4-(3′-fluorophenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3b**)

Reaction time 1.5 h; yield 68%; mp 276 °C; IR (KBr): ν 3338 (NH st), 3230 (NH st), 3149 (CH st), 3059 (CH st), 1647 (C=N st), 1615 (NH δ), 1593, 1536, 1457, 1424, 1401, 1276, 1258, 1246, 761, 742, 701 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.81–6.90 (5H, *m*, H-4, H-8, H-9 and NH_2), 6.97 (1H, *td*, *J* = 7.2, 2.3 Hz, H-7), 7.14–7.23 (3H, *m*, H-2′, H-5′ and H-6′), 7.26 (1H, *d*, *J* = 7.9 Hz, H-6), 7.43 (1H, *dd*, *J* = 7.9 Hz, J_{HF} = 10.5 Hz, H-4′), 8.47 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 64.9 (*s*, C-4), 108.1 (*s*, C-6), 113.0 (*d*, *J* = 21.8 Hz, C-2′), 115.9 (*d*, *J* = 21.1 Hz, C-4′), 116.0 (*s*, C-9), 119.1 (*s*, C-8), 121.0 (*s*, C-7), 122.0 (*d*, *J* = 2.9 Hz, C-6′), 131.0 (*s*, C-5a), 131.1 (*d*, *J* = 8.7 Hz, C-5′), 143.1 (*s*, C-9a), 143.2 (*d*, *J* = 5.1 Hz, C-1′), 153.3 (*s*, C-10a), 155.3 (*s*, C-2), 162.1 (*d*, *J* = 245.6 Hz, C-3′). Anal. Calcd. for $C_{15}H_{12}FN_5$: C, 64.05; H, 4.30; N, 24.90. Found: C, 64.36; H, 4.22; N, 24.98.

4.4. 2-Amino-4-(4′-fluorophenyl)-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3c**)

Reaction time 2 h; yield 76%; mp 242 °C (lit. 210–212 °C [2]); IR (KBr): ν 3415 (NH st), 3321 (NH st), 3224 (NH st), 3138 (CH st), 1659 (C=N st), 1605 (NH δ), 1510, 1459, 1401, 1372, 1279, 1244, 1230, 1156, 841, 762, 743 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.65 (2H, *s*, NH_2), 6.76 (1H, *d*, *J* = 7.5 Hz, H-9), 6.82 (1H, *t*, *J* = 7.5 Hz, H-8), 6.82 (1H, *s*, H-4), 6.96 (1H, *t*, *J* = 7.5 Hz, H-7), 7.23 (2H, *ddd*, *J* = 7.2, 2.3 Hz, J_{HF} = 7.7 Hz, H-3′ and H-5′), 7.25 (1H, *d*, *J* = 7.5 Hz, H-6), 7.44 (2H, *ddd*, *J* = 7.2, 2.3 Hz, J_{HF} = 5.7 Hz, H-2′ and H-6′), 8.25 (1H, *br s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 65.1 (*s*, C-4), 108.2 (*s*, C-6), 115.7 (*s*, C-9), 115.8 (*d*, *J* = 21.8 Hz, C-3′ and C-5′), 119.1 (*s*, C-8), 121.0 (*s*, C-7), 128.5 (*d*, *J* = 8.7 Hz, C-2′ and C-6′), 130.9 (*s*, C-5a), 136.7 (*s*, C-1′), 142.6 (*s*, C-9a), 153.2 (*s*, C-10a), 155.2 (*s*, C-2), 162.3 (*d*, *J* = 245.6 Hz, C-4′). Anal. Calcd for $C_{15}H_{12}FN_5$: C, 64.05; H, 4.30; N, 24.90. Found: C, 64.32; H, 4.36; N, 24.52.

4.5. 2-Amino-4-[2′-(trifluoromethyl)phenyl]-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3d**)

Reaction time 5 h; yield 64%; mp 274–275 °C; IR (KBr): ν 3403 (NH st), 3327 (NH st), 3133 (CH st), 3064 (CH st), 1656 (C=N st), 1618 (NH δ), 1591, 1528, 1462, 1425, 1313, 1276, 1248, 1168, 1125, 1106, 1038, 768, 742, 676 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.39 (1H, *d*, *J* = 7.5 Hz, H-9), 6.45 (2H, *s*, NH_2), 6.77 (1H, *t*, *J* = 7.5 Hz, H-7), 6.95 (1H, *t*, *J* = 7.5 Hz, H-8), 7.01 (1H, *s*, H-4), 7.19 (1H, *d*, *J* = 7.5 Hz, H-6), 7.27 (1H, *d*, *J* = 7.5 Hz, H-6′), 7.61 (1H, *t*, *J* = 7.7 Hz, H-4′), 7.67 (1H, *t*, *J* = 7.7 Hz, H-5′), 7.88 (1H, *d*, *J* = 7.5 Hz, H-3′), 7.90 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 62.1 (*s*, C-4), 107.4 (*s*, C-6), 116.2 (*s*, C-9), 119.3 (*s*, C-8), 121.2 (*s*, C-7), 124.2 (*q*, *J* = 272.8 Hz, CF_3), 125.9 (*q*, *J* = 30.6 Hz, C-2′), 125.9 (*q*, *J* = 5.3 Hz, C-3′), 128.0 (*s*, C-6′), 129.9 (*s*, C-4′), 130.9 (*s*, C-5a), 134.0 (*s*, C-5′), 138.3 (*q*, *J* = 4.1 Hz, C-1′), 143.3 (*s*, C-9a), 153.7 (*s*, C-10a), 154.9 (*s*, C-2). Anal. Calcd. for $C_{16}H_{12}F_3N_5$: C, 58.01; H, 3.65; N, 21.14. Found: C, 58.35; H, 3.74; N, 20.73.

4.6. 2-Amino-4-[3′-(trifluoromethyl)phenyl]-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3e**)

Reaction time 3 h; yield 75%; mp 262–263 °C; IR (KBr): ν 3440 (NH st), 3342 (NH st), 3237 (NH st), 3154 (CH st), 3059 (CH st), 1647 (C=N st), 1615 (NH δ), 1592, 1537, 1458, 1425, 1401, 1329, 1277, 1246, 1171, 1128, 1095, 1073, 764, 744, 704 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.70 (2H, *s*, NH_2), 6.83 (1H, *t*, *J* = 6.8 Hz, H-8), 6.84 (1H, *d*, *J* = 7.5 Hz, H-9), 6.96 (1H, *t*, *J* = 8.3 Hz, H-7), 6.97 (1H, *s*, H-4), 7.25 (1H, *d*, *J* = 7.9 Hz, H-6′), 7.54 (1H, *d*, *J* = 7.9 Hz, H-6), 7.62 (1H, *t*, *J* = 7.7 Hz, H-5′), 7.74 (1H, *d*, *J* = 7.5 Hz, H-4′), 7.83 (1H, *s*, H-2′), 8.36 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 64.9 (*s*, C-4), 108.0 (*s*, C-6), 116.1 (*s*, C-9), 119.1 (*s*, C-8), 120.9 (*s*, C-7), 122.9 (*q*, *J* = 3.6 Hz, C-2′), 123.9 (*q*, *J* = 272.5 Hz, CF_3), 125.8 (*q*, *J* = 3.6 Hz, C-4′), 129.4 (*q*, *J* = 32.0 Hz, C-3′), 130.0 (*s*, C-5′), 130.2 (*s*, C-6′), 131.0 (*s*, C-5a), 141.9 (*s*, C-1′), 143.3 (*s*, C-9a), 153.3 (*s*, C-10a), 155.2 (*s*, C-2). Anal. Calcd. for $C_{16}H_{12}F_3N_5$: C, 58.01; H, 3.65; N, 21.14. Found: C, 57.96; H, 3.75; N, 20.84.

4.7. 2-Amino-4-[4′-(trifluoromethyl)phenyl]-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3f**)

Reaction time 1 h; yield 72%; mp 267–268 °C; IR (KBr): ν 3464 (NH st), 3354 (NH st), 3237 (NH st), 3101 (CH st), 3058 (CH st), 1645 (C=N st), 1615 (NH δ), 1590, 1539,

1459, 1416, 1327, 1277, 1246, 1170, 1121, 1067, 1017, 845, 764, 745 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.81–6.90 (4H, *m*, J = 7.9 Hz, H-8, H-9 and NH_2), 6.97 (1H, *t*, J = 8.3 Hz, H-7), 6.98 (1H, *s*, H-4), 7.25 (1H, *d*, J = 7.9 Hz, H-6), 7.58 (2H, *d*, J = 7.9 Hz, H-2′ and H-6′), 7.78 (2H, *d*, J = 8.3 Hz, H-3′ and H-5′), 8.51 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 65.0 (*s*, C-4), 108.1 (*s*, C-6), 116.0 (*s*, C-9), 119.2 (*s*, C-8), 121.0 (*s*, C-7), 123.9 (*q*, J = 272.5 Hz, CF_3), 125.7 (*q*, J = 3.6 Hz, C-3′ and C-5′), 127.0 (*s*, C-2′ and C-6′), 129.5 (*q*, J = 31.2 Hz, C-4′), 131.0 (*s*, C-5a), 143.1 (*s*, C-9a), 144.9 (*s*, C-1′), 153.3 (*s*, C-10a), 155.3 (*s*, C-2). Anal. Calcd. for $C_{16}H_{12}F_3N_5$: C, 58.01; H, 3.65; N, 21.14. Found: C, 57.62; H, 3.75; N, 20.48.

*4.8. 2-Amino-4-[3′,5′-bis(trifluoromethyl)phenyl]-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole (**3g**)*

Reaction time 8 h; yield 65%; mp 297–298 °C; IR (KBr): ν 3440 (NH st), 3317 (NH st), 3062 (CH st), 1654 (C=N st), 1617 (NH δ), 1592, 1513, 1461, 1431, 1369, 1343, 1279, 1247, 1181, 1137, 1107, 903, 760, 746, 706, 682 cm^{-1}. ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.64 (2H, *s*, NH_2), 6.86 (1H, *t*, J = 7.5 Hz, H-8), 6.94 (1H, *d*, J = 7.2 Hz, H-9), 6.98 (1H, *t*, J = 7.5 Hz, H-7), 7.06 (1H, *s*, H-4), 7.28 (1H, *d*, J = 7.9 Hz, H-6), 7.97 (2H, *s*, H-2′ and H-6′), 8.16 (1H, *s*, H-4′), 8.26 (1H, *s*, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 64.2 (*s*, C-4), 107.9 (*s*, C-6), 116.3 (*s*, C-9), 119.3 (*s*, C-8), 121.2 (*s*, C-7), 122.9 (*q*, J = 272.8 Hz, $2CF_3$), 123.0 (*q*, J = 4.1 Hz, C-4′), 126.8 (*q*, J = 3.2 Hz, C-2′ and C-6′), 130.8 (*q*, J = 32.9 Hz, C-3′ and C-5′), 130.9 (*s*, C-5a), 143.8 (*s*, C-1′), 143.3 (*s*, C-9a), 153.1 (*s*, C-10a), 155.1 (*s*, C-2). Anal. Calcd. for $C_{17}H_{11}F_6N_5$: C, 51.14; H, 2.78; N, 17.54. Found: C, 51.24; H, 2.67; N, 17.59.

Acknowledgment

This work is supported by the Academic Research Fund from the National University of Singapore.

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