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Synthesis of *trans*-diamide derivatives from fumaryl chloride and determine DPPH scavenging activity of synthesized molecules

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Abstract: In this work, new *trans*-diamide derivatives were synthesized with the reaction between fumaryl chloride and substituted anilines. After successful synthesis of *trans*-amides, antioxidant activity of all synthesized molecules was investigated via DPPH method and calculated IC_{50} values. All *trans*-amides were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, GC-MS and FTIR spectroscopic techniques.

Keywords: Amides, DPPH method, antioxidant activity, fluorinated arenes.

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INTRODUCTION

Amides are significant groups in organic chemistry because they possess extensive biological activities such as antifungal, antioxidant etc (1–7). Also, they can be used as a precursor for synthesis of plastics, agrochemicals or known drugs in the market such as Valsartan (a), Lidocaine (b) and Bupivacaine (c) (Figure 1) (8). Thus, the synthesis of amides are one of the most important topic in academia. Beside the reaction between carboxylic acids and primary amines (8), there are many methods in the literature about amide synthesis such as Ugi reaction (9), Staudinger reaction (10) and Schmidt reaction (11). Since there are many limiting factors in the methods known scope of literature, researchers are still working to develop new methods based on amide synthesis.

In addition, fluorinated arenes are the cruicial and attractive compounds for researchers due to possessing wide application such as agrochemicals, medicine and materials science (12,13). When comparing properties of fluorine-containing compounds with their non-substituted anologues, the compounds which has fluorine groups generally show excellent chemical and biological properties (14). Thus, derivatization of arenes with the fluorine groups provide good properties to the synthesized molecules.

In this paper, new substituted *trans*-diamides which is especially containing fluorine arenes was synthesized and their antioxidant properties were investigated by using DPPH method.

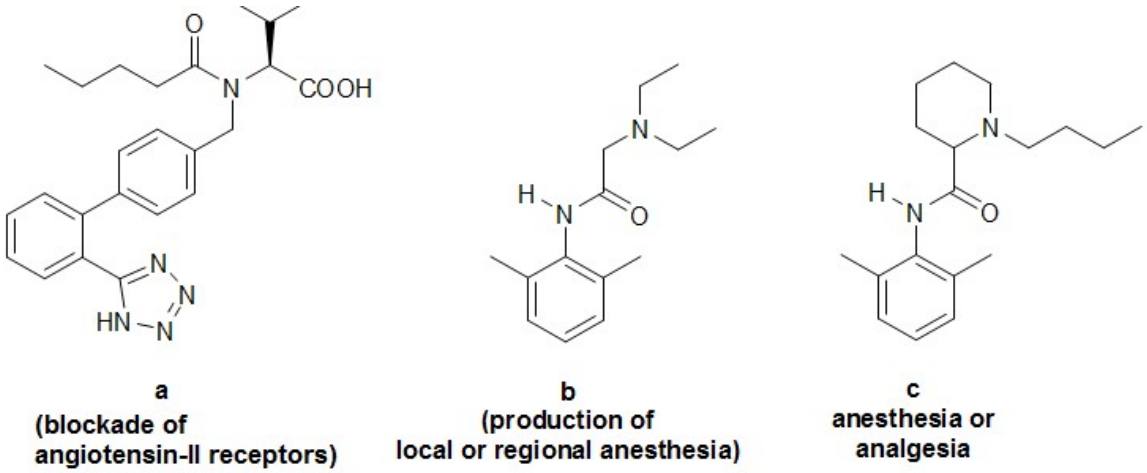


Figure 1. Some significant amide molecules having biological activity**.**

EXPERIMENTAL SECTION

Materials and Methods

Materials

Commercial chemicals were taken from Sigma-Aldrich or Merck and used directly. NMR, FT-IR and UV analyses were determined using Bruker Ultrashield Plus Biospin Avance III 400 MHz NaNoBay FT-NMR, Perkin Elmer Spectrum-100, and Chebios Optimum-One UV–Vis spectrophotometer, respectively.

General method for the synthesis

Primary amines (10.0 mmol) were dissolved in 10 mL of CH_2Cl_2 and then fumaryl chloride (5.0 mmol) was added dropwise in to the reaction mixture. After the starting materials completely consumed according to TLC analysis, the precipitated product was filtered and crystallized in methanol.

DPPH method for the investigation of antioxidant activity;

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test was investigated for all synthesized molecules according to positive controls that butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). Different concentrations (6,75–800 µg/mL) of all synthesized *trans*-diamides and positive controls were prepared in EtOH. Then, 1 mL of $1x10^{-4}$ mM DPPH solution were added into tube for each compound, and 1 mL of each sample was added on the DPPH solution. Each tube was incubated in dark for an hour and then absorbance for each sample was measured at 517 nm. The antioxidant activity was calculated with formula given below (15,16). (Equation 1)

$$\%Scavenging = \frac{A_0 - A_s}{A_0} \times 100 \quad \text{(Eq. 1)}$$

(A_o= absorbance of the control; A_s= absorbance of the sample at 517 nm)

***N*¹,*N*⁴-bis(3-fluorophenyl)fumaramide (3a, $C_{16}H_{12}F_2N_2O_2$)**

3-Fluoroaniline (1.11 g, 10.0 mmol) were dissolved in 10 mL of CH_2Cl_2 and then fumaryl chloride (0.76 g, 5.0 mmol) was added dropwise. After the starting materials come to an end according to TLC analysis, the precipitate was filtered from filter paper and crystallized in methanol. The product **3a** was obtained (1.45 g, 96%).

M.p.: 305-306 °C; **¹H NMR** (400 MHz, DMSO-d_6): δ= 10.41 (s, 2H, -NH), 7.49 (dt, J = 7.8, 1.9 Hz, 2H, ArH), 7.43 (s, 2H, -C=CH), 7.39 – 7.18 (m, 6H, ArH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ= 162.54 (s), 155.19 (d, *J* = 48.0 Hz), 152.75 (d, *J* = 48.7 Hz), 134.03 (s), 125.79 (s), 125.68 (s), 123.09 (s), 116.09 (d, *J* = 18.2 Hz), 115.57 (d, *J* = 19.3 Hz) ppm; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 124.0 (ArC-F) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3260, 3044, 2906, 1646, 1599, 1543, 1457, 1198, 750, 697 cm^{-1}; **ESI-MS** (70 eV): *m*/*z* = 304 (M^+).

***N*¹,*N*⁴-bis(4-fluorophenyl)fumaramide (3b, $C_{16}H_{12}F_2N_2O_2$)**

M.p.: 353-354 °C; **¹H NMR** (400 MHz, DMSO-d_6): δ= 10.76 (s, 2H, -NH), 7.80 – 7.74 (m, 2H, ArH), 7.50 – 7.43 (m, 2H, ArH), 7.35 (t, *J* = 8.8 Hz, 2H, ArH), 7.24 (s, 2H, -C=CH), 7.21 (t, *J* = 8.9 Hz, 2H, ArH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ= 161.99 (s), 157.14 (s), 133.95 (s), 124.95 (d, *J* = 8.7 Hz), 121.20 (d, *J* = 7.9 Hz), 116.47 (d, *J* = 23.1 Hz), 115.42 (d, *J* = 22.3 Hz) ppm; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 118.4 (ArC-F) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3252, 3046, 2924, 1650, 1619,

1502, 1408, 1237, 829, 792 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 304 (M^+).

***N^1,N^4-bis(3-(trifluoromethyl)phenyl) fumaramide* (3c, $C_{18}H_{12}F_6N_2O_2$)**

M.p.: 302-303 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 11.07 (s, 2H, -NH), 8.25 (s, 2H, ArH), 7.92 (d, *J* = 8.3 Hz, 2H, ArH), 7.63 (t, *J* = 8.0 Hz, 2H), 7.49 (s, *J* = 7.8 Hz, 2H, -C=CH), 7.47 (dd, *J* = 15.5, 7.8 Hz, 2H, ArH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.46 (s), 139.52 (s), 134.14 (s), 130.44 (s), 130.11 (s), 123.05 (s), 122.69 (s), 115.51 (dd, *J* = 7.7, 3.6 Hz), 114.94 (dd, *J* = 4.4, 2.2 Hz) ppm; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 61.4 (-CF_3) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3272, 3014, 2848, 1653, 1601, 1445, 1328, 1116, 799, 695 cm^{-1}; **ESI-MS (70 eV):** *m/z* = 401 (M^+).

***N^1,N^4-bis(4-(trifluoromethyl)phenyl) fumaramide* (3d, $C_{18}H_{12}F_6N_2O_2$)**

M.p.: 379-380 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 11.12 (s, 2H, -NH), 7.97 (d, J = 8.5 Hz, 4H, ArH), 7.74 (d, J = 8.7 Hz, 4H, ArH), 7.32 (s, 2H, -C=CH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.53 (s), 142.33 (s), 134.28 (s), 126.47 (q, *J* = 3.8 Hz), 126.11 (d, *J* = 3.8 Hz), 123.51 (dd, *J* = 73.6, 35.6 Hz), 119.44 (s) ppm; ; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 60.4 (-CF_3) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3292, 2843, 1643, 1537, 1317, 1124, 1064, 826, 692 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 401 (M^+).

***N^1,N^4-bis(2-fluoro-3-(trifluoromethyl)phenyl) fumaramide* (3e, $C_{18}H_{10}F_8N_2O_2$)**

M.p.: 261-262 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 10.74 (s, 2H, -NH), 8.35 (t, *J* = 7.4 Hz, 2H, ArH), 7.59 (t, *J* = 6.7 Hz, 2H, ArH), 7.45 (t, *J* = 8.0 Hz, 2H, ArH), 7.46 (s, 2H, -C=CH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.66 (s), 148.81 (d, *J* = 1.6 Hz), 146.33 (d, *J* = 1.2 Hz), 135.84 (d, *J* = 11.4 Hz), 134.05 (s), 128.79 (s), 127.10 (d, *J* = 10.5 Hz), 124.88 (d, *J* = 4.5 Hz), 113.75 (q, *J* = 4.7 Hz) ppm; ; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 126.7 (ArC-F), 59.9 (-CF_3) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3251, 2811, 1643, 1537, 1484, 1322, 1132, 796, 733 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 437 (M^+).

***N^1,N^4-bis(2-fluoro-4-(trifluoromethyl)phenyl) fumaramide* (3f, $C_{18}H_{10}F_8N_2O_2$)**

M.p.: 336-337 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 10.74 (s, 2H, -NH), 8.42 (t, *J* = 8.1 Hz, 2H, ArH), 7.80 (dd, *J* = 11.0, 1.7 Hz, 2H, ArH), 7.64 (d, *J* = 8.5 Hz, 2H, ArH), 7.52 (s, 2H, -C=CH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.82 (s), 150.55 (s), 148.18 (s), 140.19 (d, *J* = 13.1 Hz), 134.35 (s), 123.71 (d, *J* = 1.4 Hz), 122.05 (p, *J* = 3.0 Hz), 115.63 (d, *J* = 5.3 Hz), 112.29 (q, *J* = 3.7 Hz) ppm; ; **^{19}F NMR (376 MHz, DMSO-d_6):** δ = 122.2 (ArC-F), 60.6 (-CF_3) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3298, 3021, 1659, 1623, 1540, 1430, 1325, 1121, 887, 651 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 437 (M^+).

***N^1,N^4-bis(2-cyanophenyl)fumaramide* (3g, $C_{18}H_{12}N_4O_2$)**

M.p.: 338-339 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 10.94 (s, 2H, -NH), 7.89 (dd, *J* = 7.8, 1.1 Hz, 2H, ArH), 7.75 (dtd, *J* = 9.3, 8.3, 1.3 Hz, 4H, ArH), 7.45 (td, *J* = 7.7, 1.4 Hz, 2H, ArH), 7.37 (s, 2H, -C=CH) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 162.54 (s, C=O), 139.55 (s, ArC), 133.35 (s, ArC), 126.26 (s, ArC), 125.56 (s, ArC), 118.04 (s, ArC), 116.66 (s), 107.42 (s), 93.64 (s) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3267, 3036, 2906, 2233, 1648, 1542, 1451, 1335, 995, 773, 675 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 315 (M^+).

***N^1,N^4-bis(4-methoxyphenyl)fumaramide* (3h, $C_{18}H_{18}N_2O_4$)**

M.p.: 270-271 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 10.49 (s, 2H, -NH), 7.66 (d, *J* = 9.1 Hz, 4H, ArH), 7.35 (d, *J* = 9.0 Hz, 4H, ArH), 7.18 (s, 2H, -C=CH), 3.76 (s, 6H, -OCH_3); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 161.72 (s), 155.66 (s), 133.75 (s), 124.29 (s), 120.90 (s), 114.84 (s), 55.21 (s) ppm; **FTIR (KBr):** $\bar{\nu}$ = 3274, 3049, 2837, 1634, 1531, 1508, 1245, 1164, 1023, 830, 663 cm^{-1}; **ESI-MS** (70 eV): *m/z* = 325 (M^+).

RESULTS AND DISCUSSION

Reactions between 1 equivalent fumaryl chloride **1** and 2 equivalent different primary amines **2a-h** was investigated and obtained substituted *trans*-diamides with high yield (Figure 2). Reaction with the *ortho*-substituted primary amines gave lower yield than *meta*- or *para*-subtituted primary amines due to the sterical effect on the amine group (Table 1).

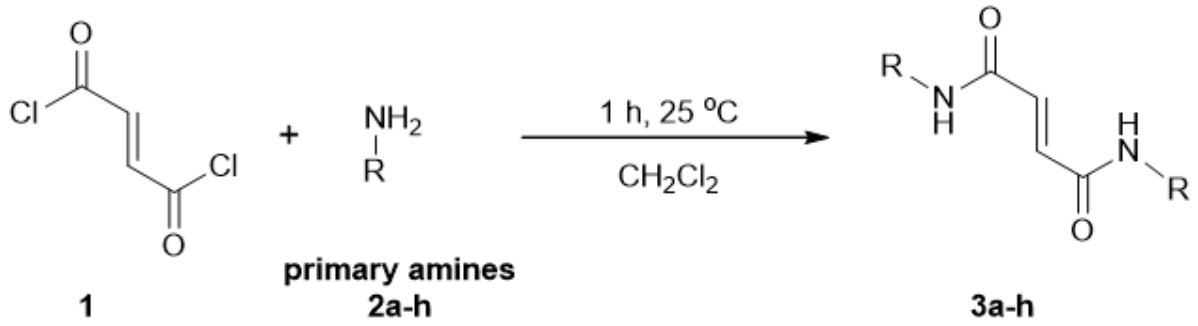
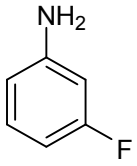
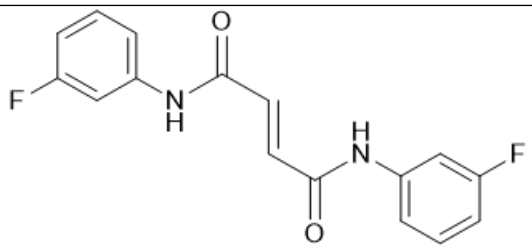
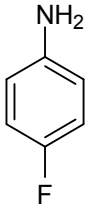
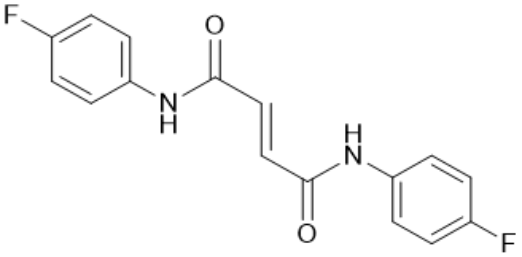
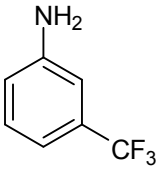
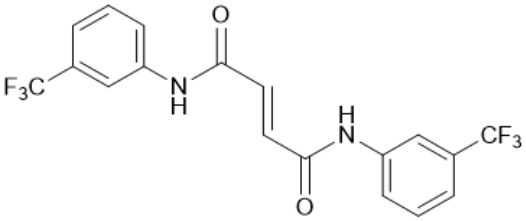
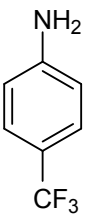
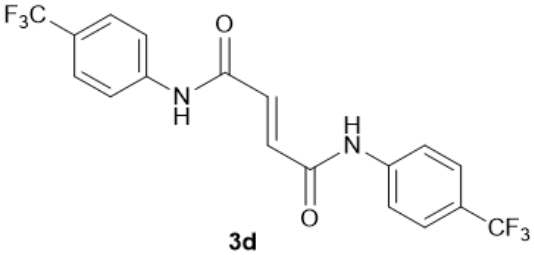
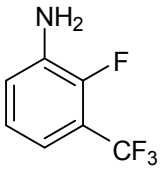
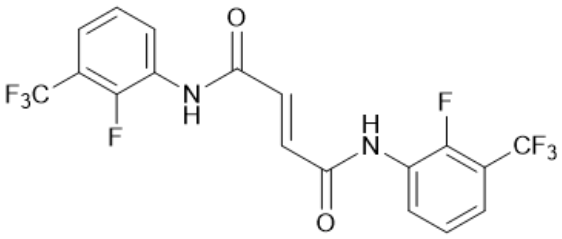
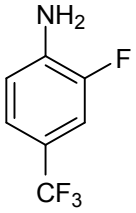
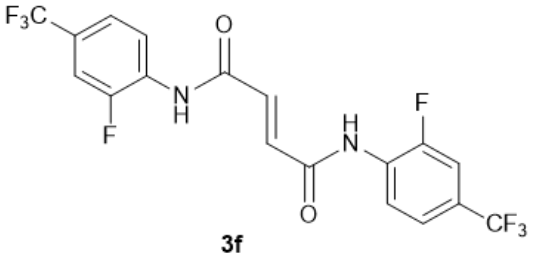
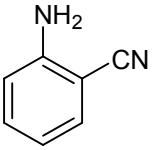
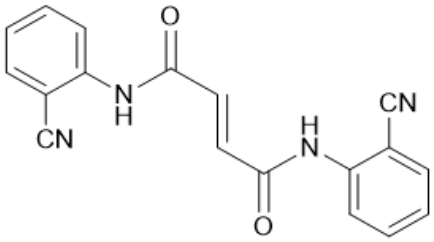
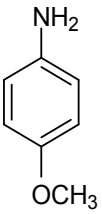
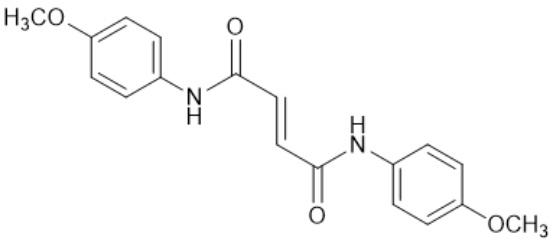


Figure 2. General reaction for the synthesis of *trans*-diamides.

Table 1. Synthesis of *trans*-diamides **3a-h.**

Entry	Acyl chloride	Amines	Product	Yield %
1	**1**	 **2a**	 **3a**	96
2	**1**	 **2b**	 **3b**	95
3	**1**	 **2c**	 **3c**	92
4	**1**	 **2d**	 **3d**	96
5	**1**			77

		 **2e**	 **3e**	
6	**1**	 **2f**	 **3f**	84
7	**1**	 **2g**	 **3g**	82
8	**1**	 **2h**	 **3h**	97

All *trans*-diamide structures were characterized with spectroscopic analyses (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, LC-MS, FT-IR). In the ^{1}H-NMR spectra of **3a-h**, it is clearly shown that, -NH protons gave singlets in the area between δ 10.41-11.12 ppm, which approved with known similar compounds in the literature (17,18). Protons of double bond (**3a-h**) were observed as singlets in the region between δ 7.18-7.53 ppm. While the signal of aromatic protons was observed between δ 7.21-8.42 ppm (17,18), methoxy protons of the compound **3h** were observed at 3.76 ppm as a singlet (19). In addition, in the ^{13}C NMR spectra of compounds **3a-h**, the signal of carbonyl carbon appeared between δ 163-161 ppm and the peaks of aromatic/olefinic carbons appeared the area between δ 107.42-155.66 ppm. Also, the signal of nitrile carbon of compound **3g** and the methoxy carbon of compound **3h** appeared at δ 93.64 ppm and δ 55.21 ppm respectively. When ^{19}F NMR of compound **3a-f** was examined, it was seen that characteristic signals of –F (between δ 118.38 – 126.64 ppm) and -CF_3 (between δ 59.88 – 61.40 ppm) groups were in expected regions (see Supporting Information) (20). Also, NMR results were supported with LC-MS and FT-IR analysis. When the FTIR spectra was examined, the –N-H stretching bands of **3a-h** observed between 3272–3251 cm^{-1}. The Ar-H stretching bands and –C=O stretching bands of **3a-h** was observed between 3049–3014 cm^{-1} and 1659–1634 cm^{-1}, respectively. In addition, the –CN band of compound **3g** was observed at 2233 cm^{-1}.

After the successful synthesis of *trans*-diamide derivatives, we focused on to investigate DPPH scavenging activity of all the synthesized molecules. Free radicals that are generated permanently in the body included unpaired electrons and, these electrons can easily interact

with biomolecules (15). Common diseases like cardiovascular diseases and cancer, have been occurred due to free radical damage. Thus, synthesis of antioxidant molecules that can convert the radicals to stable compound are so important. Because of these properties, antioxidant molecules have affirmative effects on health (15). DPPH method has been commonly used for investigating the antioxidant activity. This technique easily gives an antiradical potential of molecule with UV measurement at 515 nm (21).

For this purpose, different concentrations of each synthesized molecule and positive controls were prepared (12.5, 25, 50, 100, 200, 400, 800 µg/mL) and added to DPPH solution which was prepared freshly. After 30 minutes of incubation in the dark, $_{515}$UV measurements was taken for each concentration and the IC_{50} value was calculated as 302.52 µg, 304.17 µg, 266.74 µg, 251.46 µg, 315.51 µg, 402.44 µg, 325.75 µg, 595.27 µg, 68.65 µg and 39.46 µg for compound **3a**, **3b**, **3c**, **3d**, **3f**, **3g**, **3h**, BHT, and BHA, respectively. According to these results, all synthesized molecules showed lower DPPH scavenging activity when compared with positive controls BHT and BHA. Also, these results showed that the antioxidant activity of synthesized molecules increased in order of 3h<3f<3g<3e<3b<3a<3d<3c<BHT<BHA.

Substituted anilines with electron withdrawing/deactivating group (-CF_3) showed better DPPH scavenging activity than substituted anilines with weakly deactivating (-F) or electron donating/activating (-OCH_3) group. Also, when DPPH scavenging activity of compounds which substituted with the same group was examined, the *meta*- substituted anilines showed better activity than *para*- substituted ones. (3b<3a or 3d<3c)

Table 2. The IC_{50} values of *trans*-diamides and positive controls.

Compound	IC_{50} (µg)
3a	302.52
3b	304.17
3c	251.46
3d	266.74
3e	315.51
3f	402.44
3g	325.75
3h	595.27
BHT	68.65
BHA	39.46

CONCLUSION

In summary, new *trans*-diamides were synthesized with the reaction between primary amines and fumaryl chloride. In addition, the DPPH scavenging activity for each synthesized molecule was investigated and obtained moderate results compared to positive controls BHT and BHA.

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REFERENCES

1. Sathe PA, Karpe AS, Parab AA, Parade BS, Vadagaonkar KS, Chaskar AC. Tandem synthesis of aromatic amides from styrenes in water. Tetrahedron Lett. 2018 Jul;59(29):2820–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0040403918307639

2. Srivastava V, Singh PK, Singh PP. Visible light photoredox catalysed amidation of carboxylic acids with amines. Tetrahedron Lett. 2019 Jan;60(1):40–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0040403918313972

3. Han Q, Xiong X, Li S. An efficient, green and scale-up synthesis of amides from esters and amines catalyzed by Ru-MACHO catalyst under mild conditions. Catal Commun. 2015 Jan;58:85–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1566736714003483

4. Hong G, Wu S, Zhu X, Mao D, Wang L. Peroxide-mediated direct synthesis of amides from aroyl surrogates. Tetrahedron 2016 Jan;72(3):436–41. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0040402015302477

5. Lanigan RM, Starkov P, Sheppard TD. Direct Synthesis of Amides from Carboxylic Acids and Amines Using B(OCH 2 CF 3) 3. J Org Chem. 2013 May 3;78(9):4512–23. Available from: https://pubs.acs.org/doi/10.1021/jo400509n

6. Ghorpade SA, Sawant DN, Sekar N. Triphenyl borate catalyzed synthesis of amides from carboxylic acids and amines. Tetrahedron 2018 Nov;74(48):6954–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0040402018312365

7. Cadoni R, Porcheddu A, Giacomelli G, De Luca L. One-pot synthesis of amides from aldehydes and amines via C-H bond activation. Org Lett. 2012;

8. Valeur E, Bradley M. Amide bond formation: beyond the myth of coupling reagents. Chem Soc Rev. 2009;38(2):606–31. Available from: http://xlink.rsc.org/?DOI=B701677H

9. Ugi I. The ?-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. Angew Chemie Int Ed English 1962 Jan 27;1(1):8–21. Available from: http://doi.wiley.com/10.1002/anie.196200081

10. Damkaci F, DeShong P. Stereoselective Synthesis of α- and β-Glycosylamide Derivatives from Glycopyranosyl Azides via Isoxazoline Intermediates. J Am Chem Soc. 2003 Apr;125(15):4408–9. Available from: https://pubs.acs.org/doi/10.1021/ja028694u

11. Ribelin T, Katz CE, English DG, Smith S, Manukyan AK, Day VW, et al. Highly Stereoselective Ring Expansion Reactions Mediated by Attractive Cation-π Interactions. Angew Chemie Int Ed. 2008 Aug 4;47(33):6233–5. Available from: http://doi.wiley.com/10.1002/anie.200801591

12. Fang X, Huang Y, Chen X, Lin X, Bai Z, Huang K-W, et al. Preparation of fluorinated biaryls through direct palladium-catalyzed coupling of polyfluoroarenes with aryltrifluoroborates. J Fluor Chem. 2013 Jul;151:50–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022113913001413

13. Politanskaya L, Petyuk M, Tretyakov E. Transformation of fluorinated 2-alkynylanilines by various catalytic systems. J Fluor Chem. 2019 Oct;109394. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022113919303185

14. Li X, Liu J, Li X, Liu H, Liu H, Li Y, et al. Recent advance in the synthesis of (1,1-difluoroethyl)arenes. J Fluor Chem. 2018 Dec;216:102–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022113918303932

15. Bursal E, Aras A, Kılıç Ö, Taslimi P, Gören AC, Gülçin İ. Phytochemical content, antioxidant activity, and enzyme inhibition effect of Salvia eriophora Boiss. & Kotschy against acetylcholinesterase, α-amylase, butyrylcholinesterase, and α-glycosidase enzymes. J Food Biochem. 2019 Mar;43(3):e12776. Available from: http://doi.wiley.com/10.1111/jfbc.12776

16. Güzel S, Özay Y, Kumaş M, Uzun C, Özkorkmaz EG, Yıldırım Z, et al. Wound healing properties, antimicrobial and antioxidant activities of Salvia kronenburgii Rech. f. and Salvia euphratica Montbret, Aucher & Rech. f. var. euphratica on excision and incision wound models in diabetic rats. Biomed Pharmacother. 2019 Mar;111:1260–76. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0753332218362073.

17. Ding Y, Zhang X, Zhang D, Chen Y, Wu Z, Wang P, et al. Copper-catalyzed oxidative amidation between aldehydes and arylamines under mild conditions. Tetrahedron Lett. 2015 Feb;56(6):831–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0040403914021911

18. Rzhevskiy SA, Ageshina AA, Chesnokov GA, Gribanov PS, Topchiy MA, Nechaev MS, et al. Solvent- and transition metal-free amide synthesis from phenyl esters and aryl amines. RSC Adv. 2019;9(3):1536–40. Available from: http://xlink.rsc.org/?DOI=C8RA10040C

19. Agirbas H, Kemal B, Budak F. Synthesis and structure–antibacterial activity relationship studies of 4-substituted phenyl-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-thiones. Med Chem Res. 2011 Nov 10;20(8):1170–80. Available from: http://link.springer.com/10.1007/s00044-010-9457-4

20. Yılmaz MK, Güzel B. Iminophosphine palladium(II) complexes: synthesis, characterization, and application in Heck cross-coupling reaction of aryl bromides. Appl Organomet Chem. 2014 Jul;28(7):529–36. Available from: http://doi.wiley.com/10.1002/aoc.3158

21. Parhiz H, Roohbakhsh A, Soltani F, Rezaee R, Iranshahi M. Antioxidant and Anti-Inflammatory Properties of the Citrus Flavonoids Hesperidin and Hesperetin: An Updated Review of their Molecular Mechanisms and Experimental Models. Phyther Res. 2015 Mar;29(3):323–31. Available from: http://doi.wiley.com/10.1002/ptr.5256