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<AT>Synthesis of new (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones and (trifluoromethyl)benzo[5,6][1,2,4]triazino [1,2-b]phthalazine-8,13-diones <AU>Mahin Ramezani, Ali Darehkordi^{*} ##Email##darehkordi@vru.ac.ir ##/Email## ##Email##adarehkordi@yahoo.com##/Email## <AEE>Department of Chemistry, Faculty of Science, Vali e, Asr University of Pafsanian

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<ABS-Head><ABS-HEAD>Graphical abstract

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<ABS-HEAD>Highlights • new (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2a][1,2,4]triazine-1,3(2H)-diones and (trifluoromethyl)benzo[5,6][1,2,4]triazino [1,2b]phthalazine-8,13-diones were prepared •Simple procedure• High reaction yields. •New bioactive Trifluoromethyl heterocyclic compounds

<ABS-HEAD>Abstract

<ABS-P>In this paper we investigated reactions of urazole and phthalazine with N-(aryl)-2,2,2-

trifluoroacetimidoyl chloride derivatives.

<ABS-P><ST>Results</ST> showed that when imidoyl chloride derivative has a fluorine atom at ortho position (**3a-c**), in two steps under a S_Ni mechanism and then S_NAr reaction mechanism produce ayl-5-(trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones (**4a-c**) and 6-(trifluoromethyl)benzo[5,6][1,2,4]triazino[1,2-b]phthalazine-8,13-diones (**4i,4j**) in good to excellent yields. In the other imidoyl derivatives (**3d-h** and **3i,3j**) under these conditions cyclization reaction does not occur and therefore produce 1-aryl-2,2,2-trifluoromethyl)-4-phenyl-1,2,4-triazolidine-3,5-diones (**4d-h**) and 2-(2,2,2-trifluoro-1-(arylimino)ethyl)-2,3dihydrophthalazine-1,4-diones(**4k,4l**) (non-cyclic products) in good to excellent yields. <KWD>Keywords: *N*-(aryl)-2,2,2-trifluoroacetimidoyl chloride; urazoe; phthalazine; (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-dione; (trifluoromethyl)benzo[5,6] [1,2,4]triazino[1,2-b]phthalazine-8,13-diones

Introduction

The preparation of novel heterocyclic compounds has always been important and interesting because of their wide applications. Among these compounds, nitrogen-containing heterocyclic compounds occur very widely in natural products and are essential to life, and their applications in biochemical, agrochemicals, and functional materials are very important.^{1, 2a-d} Heterocycles containing a urazole nucleus and a hydrazine moiety are of interest because they have showed useful biological activities and use in clinical process (**Fig. 1**).^{3,4a-c} Also urazole derivatives and fused phthalazines exhibit various biological activity such as anticonvulsant,⁵ fungicidal ^{6, 7} antimicrobial,⁸ anticonvulsant,⁹ anticancer,¹⁰ and anti-inflammatory activities.¹¹ Therefore, synthesis and development of new synthetic methods for preparing heterocycles containing urazole or phthalazine ring moiety have attracted much interest in organic and medicinal chemistry recently. ^{4a-c, 12, 13}

The synthesis of biologically active organofluorine heterocyclics has received more attention in the medicinal chemistry and materials sciences. Among these derivatives synthesis and development of new methods for preparation of CF_3 containing heterocyclic compounds are more attention, because of their physical and pharmaceutical properties and using in industry, medicinal and agriculture.^{14, 15}

Combination of organofluorine compounds with urazole or phthalazine ring can be improve biological properties and influences the electron density distribution in organic and bioorganic molecules. The electron-withdrawing properties of CF₃ group enhanced the electrophilicity in functional of molecule^{16a-d} and therefore makes some partially fluorinated compounds valuable precursor for synthesis of new heterocyclic containing fluorine atom.¹⁷⁻²⁰

Due to the important of urazole and phthalazide derivatives and organofluorine compounds especially trifluoromethylated heterocyclics, in chemistry, drug and medicinal chemistry and in continuation of our research on the synthesis of trifluoromethylated compounds from imidoyl halides ²¹⁻²⁵, the present work aimed at the synthesis of fused trifluoromethylated heteropolycyclic nitrogen systems containing a fused urazole or phthalazide moiety starting from imidoyle chlorides.

Result and discussion

Imidoyl chlorides (**1a-j**) have been prepared by refluxing a mixture of trifluoroacetic acid (TFA), primary amines, in carbon tetrachloride in the presence of triethylamine and triphenylphosphine in one pot reaction. Work-up and distillation provided the desired imidoyl chlorides from good to excellent yields.^{26, 27}

In our initial studies, urazole (1) and N-(2,6-difluorophenyl)-2,2,2-trifluoroacetimidoyl chloride **3a** were chosen as model substrates to optimize the reaction parameters. Firstly the reaction was carried out with 1 mmol urazole (1) and 1 mmol N-(2,6-difluorophenyl)-2,2,2-

trifluoroacetimidoyl chloride (**3a**) in DMF as solvent and potassium carbonate (K_2CO_3) as a base. After 24 h at the room temperature and 18 h under reflux conditions did not give the desired product and *N*-(2,6-difluorophenyl)-2,2,2-trifluoroacetimidoyl chloride was hydrolyzed to *N*-(2,6-difluorophenyl)-2,2,2-trifluoroacetamide based on analytical and spectral data (Table 1, entry 1,2). Also reaction was performed in THF as solvent in present of sodium hydride (NaH) as the base at room temperature or under reflux conditions. After 18 h at the room temperature and 12 h under reflux hydrolyzed product was obtained (Table 1, entry 3,4). Therefore this reaction was repeated with 1 mmol of *N*-(2,6-difluorophenyl)-2,2,2-trifluoroacetimidoyl chloride (**3a**), 1 mmol of urazole (**2**) in acetonitrile as solvent in the presence of sodium hydride (NaH) as the base at room temperature and under reflux conditions. The results are summarized in table 1. It was observed that, NaH as base and acetonitrile as solvent under reflux conditions shown excellent product yield (Table 1, entry 6).

Prompted by this success, we extended the reaction of urazole with a wide range of other substituted imidoyl chloride compounds under similar conditions, furnishing the corresponding product in good to excellent yields (Table 2).

A as a mentioned in table 1 (entry 6), optimized conditions for synthesis of 4-phenyl-1-(2,2,2-trifluoro-1-(arylimino)ethyl)-1,2,4-triazolidine-3,5-diones (**4d-c**) and 2-phenyl-5- (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones (**4a-c**) by treatment of N-(aryl)-2,2,2-trifluoroacetimidoyl chlorides with urazole (**1**) is refluxing in dry acetonitrile in present of sodium hydride as base. This promoted us to a similar strategy on utilizing 2,3-dihydrophthalazine-1,4-dione instead of urazole. Thus we carried out a reaction utilizing equimolar quantities of 2,2,2-trifluoro-N-(2-fluorophenyl)acetimidoyl chloride (**3c**),

2,3-dihydrophthalazine-1,4-dione (2) in 10 mL dry acetonitrile in the same conditions. The product **4i** was not detected in this conditions (Table 3, entry 1). However, the products obtained was identified as the 2,2,2-trifluoro-N-(2-fluorophenyl)acetamide (hydrolysis product) based on analytical and spectral data. In an attempt to produce and improve the yield of **4i**, the above reactions were carried out in a variety of solvents such as tetrahydrofuran, dimethylformamide, tetrahydrofuran-dimethylformamide, and different bases such as NaH, K₂CO₃, and Et₃N at reflux conditions. The results are summarized in table 3. Therefore, the optimal reaction conditions were identified as follows: dry tetrahydrofuran as a solvent, triethylamine as a base and reflux conditions (Table 3, entry 6).

After the optimal reaction conditions were established, we continued to explore the generality of

the protocol. The outcome was listed in Table 4.

All of the products were characterized by FT-IR, ¹H- ¹³C-NMR, ¹⁹F-NMR spectra and elemental

analysis. Also some of the structure compounds were confirmed with use of MS and 2-D-NMR

(HSQC technique).

In the ¹HNMR spectrum of 8-fluoro-2-phenyl-5-(trifluoromethyl)-1H

benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-dione (**4a**) the aromatic protons of phenyl urazol appear in the region of δ 7.50-7.62 ppm. All of these protons (C1, C2, C6, C3, and C5) are correlating to each other in their corresponding correlation spectroscopy (**Fig. 2**, and **Fig 4**). The ¹H-NMR spectrum of compound **4a** (**Fig 2**) exhibited three signals, a triplet of doublets at 7.29 for the proton 19 (*J*= 8.7, 2.9 Hz), a doublet of doublets at 7.36 for the proton 21 (*J*= 8.8, 2.9 Hz) and a doublet of doublets at 7.59 for the proton 18 (*J*= 9.0, 5.2 Hz) that the match with chemical structure of compound **4a**.

The chemical shifts of para-substituted fluorobenzenes have a reasonable correlation with the σ_p values of the substituents for carbons in ¹³C-NMR spectrum; the more electron-withdrawing substituents leading to greater deshielding of the p-fluorine and rough correlation for orthosubstituted and meta-substituted.²⁸

A fluorine substituent on benzene has a characteristic effect upon the ¹³C-NMR spectrum of benzene, and it couples in a distinctive and highly consistent manner with the ipso, ortho, meta, and para carbons. The F coupling to carbon can be vary considerably for the carbon directly substituted (ipso), depending on its substitution environment, but it is always very large.²⁹ In the ¹³C-NMR spectrum (**Fig. 3**) the C20 providing the largest observed effect, deshielding carbon at δ 159.59 with coupling constant of 243.4 Hz and carbons in ortho position observed effects at 117.71 (²*J*_{C-*F*}= 23.0 Hz, C19) and δ 115.51 (²*J*_{C-*F*}= 16.2 Hz, C21), meta position observed effects at δ 115.92 (³*J*_{C-*F*}= 7.8 Hz, C18) and δ 130.44 (C15) ppm and para position observed effects at δ 125.78 (⁴*J*_{C-*F*}= 3.2 Hz, C14) ppm. Also the aromatic carbons of phenyl urazol appear between 127.51-130.55 ppm. The ¹³C-NMR spectrum (**Fig. 3**) shows that the amide carbonyl carbons appear at high frequency region at δ 145.35 and 142.28 ppm. The aromatic carbons and its corresponding protons are in correlation in their heteronuclear single quantum correlation (HSQC) spectrum (**Fig. 4**). Also all of the protons are correlating with corresponding carbons in their single quantum correlation spectrum. The carbons, which have no protons, are not correlating with any other proton nuclei.

The carbon signals deriving from CF_3 groups are often difficult to discern and thus sometimes are unfortunately not even reported. Trifluoromethyl exhibited a very little variation quartet at 116.73 ppm with coupling constant of 275.9 Hz and C17-CF₃ exhibited a quartet at 136.72 ppm

with coupling constant of 41 Hz (**Fig 3**). Also ¹⁹F-NMR in figure 5 exhibited the CF₃ group at - 68.16 and the F group attached to the benzene ring at -113.60 ppm.

Due to the ambident nature of the nucleophile formed in the reaction, nitrogen nucleophile can perform the S_NAr reaction, and the reaction course is very dependent on the X substituents on the aromatic ring and its position that showed in scheme1. In the other hand compounds **4d-4h** and **4j**, **4l** are different. These compounds cannot undergo S_NAr reaction. For example the IR spectrum of compound **4d** exhibit an absorption bands at 3336 cm⁻¹ which is related to NH group and also chemical shift data and coupling constant in NMR showed which in these compounds, cyclocondensation reaction don't occurred. Also Mass spectra were indicated this results. A suggested mechanism for cyclization reaction is shown in scheme 2. We assume that initially immino group of imidoyl is attacked by nucleophilic urazole in present of sodium hydride as a base to replace of chlorine atom by nitrogen under S_Ni mechanism. Subsequent attack of the another nitrogen atom of urazole on the fluoro atom on the aromatic ring under S_NAr reaction mechanism gives the 8-fluoro-2-phenyl-5-(trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-dione (**4a**) (Scheme 2).

Conclusion

We have synthesis a novel series of (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2a][1,2,4]triazine-1,3(2H)-diones and (trifluoromethyl)benzo[5,6][1,2,4]triazino[1,2b]phthalazine-8,13-diones by reaction of urazole and phthalzine with *N*-(aryl)-2,2,2trifluoroacetimidoyl chlorides in good to excellent yields. By this reaction we have developed a new method for synthesis of trifluoromethylated heterocyclic compounds using imidoyl chlorides and 1,2-N,N bi-nucleophile. I hope the presented synthesis provides access to preparation of bioactive fluoroheterocycli compounds.

Experimental

General

¹H-NMR spectra were recorded in CDCl₃ and DMSO-*d*₆ on a Bruker model DRX-400 AVANCE spectrometer (400 MHz) with TMS as internal standard. ¹⁹F-NMR spectra were taken on a Bruker AM-400 (376.27 MHz) spectrometer using CFCl₃ as external standard. ¹³C-NMR spectra were taken a Bruker model DRX-400 AVANCE (100 MHz) spectrometer. Only compound 4h were recorded on a Bruker model DRX-300 AVANCE (¹H: 300, ¹³C: 75, F: 282.20 MHz) NMR spectrometer. Chemical shifts are given in d relative to TMS, the coupling constants J are given in Hz and spectra were recorded in parts per million (ppm). Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were obtained on a Thermo scientific, Nicolet is10 FT-IR spectrometer. Peaks are reported in wave numbers (cm⁻¹). Mass spectra were recorded on an Agillent, 6410 QQQ, LC mass spectrometer (direct injection). Element analyses (CHN) were performed with a EUROVECTOR EuroEA3000 CHNSO analyzer.

General procedure for the synthesis of 4a-g, from urazole (1) with aceteimidoyle chloride derivatives (3).

A mixture of urazole 1 (1 mmol), sodium hydride (2 mmol) in dry acetonitrile (5 mL) was stirred at the ambient temperature for 10 min. Then a solution of aceteimidoyl chloride derivative 3 (1 mmol) in dry acetonitrile (5 mL) was added dropwise and the reaction mixture was heated under reflux conditions. After completion of the reaction, as indicated by TLC, the solvent was evaporated at reduced pressure; a precipitate formed was washed with n-hexane and was recrystallized from 95% ethanol for compounds **4a-c** or was purified by plate chromatography on silica gel (n-hexane/ethyl acetate 6:2) for compounds **4d-h**.

8-fluoro-2-phenyl-5-(trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-

1,3(2H)-dione (4a).

Yellow solid. mp 176-178 °C. IR (KBr, cm⁻¹): 2924, 1796, 1784, 1732, 1649. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.95 (dd, *J* = 9.0, 5.2 Hz, 1H), 7.67–7.47 (m, 5H), 7.36 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.29 (td, *J* = 8.7, 2.9 Hz, 1H). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 159.42 (d, *J*_{C-F} = 243.4 Hz, C20, C-F), 145.35 (C=O), 142.27 (C=O), 136.72 (q, *J*_{C-C-F} = 41.1 Hz, C17, <u>C</u>-CF₃), 130.55, 130.44, 129.77 (C1, C2, C6), 127.51(C3, C5), 125.78 (d, *J* = 3.2 Hz, C14), 117.71 (d, *J* = 23.0 Hz, C19), 116.73 (q, *J*_{C-F} = 275.9 Hz, C23, C-<u>CF₃</u>), 115.92 (d, *J* = 7.8 Hz, C18), 115.51 (d, *J* = 16.2 Hz, C21). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -68.16 (s, 3F, CF₃), -113.60 (m, 1F). Anal. Calcd for C₁₆H₈F₄N₄O₂ (364.26): C, 52.76; H, 2.21; N, 15.38; Found: C, 52.70; H, 2.02; N, 15.29 %.

9-fluoro-2-phenyl-5-(trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-

1,3(2H)-dione (4b).

Yellow solid. mp 158-160 °C. IR (KBr, cm⁻¹): 2923, 1796, 1784, 1737, 1645. ¹H-NMR (400 MHz, CDCl₃): δ 7.92 (dd, J = 9.2, 2.7 Hz, 1H), 7.63-7.47 (m, 5H), 7.39 (dd, J = 8.7, 5.5 Hz, 1H), 6.89 (ddd, J = 8.7, 7.9, 2.7 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 163.35 (d, J_{C-F} = 253.6 Hz, C-F), 154.40 (q, J_{C-C-F} = 31.2 Hz, <u>C</u>-CF₃), 151.40 (C=O), 150.64 (C=O), 144.09, 137.93 (d, J = 8.1 Hz), 135.94, 134.58, 130.36 (d, J = 9.7 Hz), 129.52(3C), 125.97(2C), 117.61 (q, J_{C-F} = 277.4 Hz, C-<u>CF₃</u>), 113.09 (d, J = 22.9 Hz), 103.50 (d, J = 31.2 Hz). ¹⁹F-NMR (376.27 MHz, CDCl₃): δ -68.06 (s, 3F, CF₃), -103.82 (m, 1F). Anal. Calcd for C₁₆H₈F₄N₄O₂ (364.26): C, 52.76; H, 2.21; N, 15.38. Found: C, 52.73; H, 2.16; N, 15.34%.

2-phenyl-5-(trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-dione (4c).

Yellow solid. mp 162-165 °C. IR (KBr, cm⁻¹): 2925, 1784, 1731, 1646. ¹H-NMR (400 MHz, CDCl₃): δ 8.14 (dd, J = 8.1, 1.3 Hz, 1H), 7.65–7.46 (m, 4H), 7.41 (dd, J = 7.8, 1.5 Hz, 1H), 7.35 (td, J = 7.9, 1.5 Hz, 1H), 7.21 (td, J = 7.7, 1.3 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ 144.12 (C=O), 141.03(C=O), 134.96 (q, J_{C-C-F} = 42.4 Hz, <u>C</u>-CF₃), 132.49, 131.48, 129.77, 129.47 (2C), 129.33, 128.68, 128.26, 126.66, 126.03 (2C), 117.82 (q, J_{C-F} = 276.4 Hz, C-<u>CF₃</u>), 114.71. ¹⁹F-NMR (376.27 MHz, CDCl₃): δ -68.10 (s, 3F, CF₃). MS (m/z): calcd for C₁₆H₉F₃N₄O₂ [M⁺] 346.0736, found: 346.2030.

1-(1-(2-bromophenylimino)-2,2,2-trifluoromethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione

(**4d**).

White solid. mp 210-215 °C. IR (KBr, cm⁻¹): 3336, 3071, 1790, 1758, 1696, 1610. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.27-7.55 (m, 9H, Ar), 10.02 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 158.53 (q, *J*_{C-F} = 30.7 Hz, <u>C</u>-CF₃), 154.30 (C=O), 151.99 (C=O), 138.53, 134.46, 134.28, 129.34, 128.81 (2C), 128.57, 126.16, 125.84 (2C), 125.78, 123.62 (q, *J*_{C-C-F} = 274.0 Hz, C-<u>CF₃</u>), 119.28. ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -73.54 (s, 3F, CF₃). MS (m/z): calcd for C₂₀H₁₂N₄O₆ (M+H⁺) 404.0736, found: 404.0734.

1-(1-(4-chlorophenylimino)-2,2,2-trifluoromethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (4e).

Yellow solid. mp 287-292 °C. IR (KBr, cm⁻¹): 3400, 1789, 1757, 1705, 1649. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.25-7.66 (m, 9H), 9.98 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 154.06 (q, *J*_{C-C-F} = 29.0 Hz, <u>C</u>-CF₃), 151.85 (C=O), 150.73 (C=O), 145.93, 134.44, 129.97 (2C), 129.03, 128.79 (2C), 127.27 (2C), 126.79, 126.19 (2C), 123.59 (q, *J*_{C-F} = 261.0 Hz, C-<u>CF₃</u>). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -73.52 (s, 3F, CF₃). Anal. Calcd for C₁₆H₁₀ClF₃N₄O₂ (382.73): C, 50.21; H, 2.63; N, 14.64. Found: C, 50.15; H, 2.60; N, 14.60%. 4-phenyl-1-(2,2,2-trifluoro-1-((3-(trifluoromethyl)phenyl)imino)ethyl)-1,2,4-triazolidine-3,5-dione (4f).

Cream solid. IR (KBr, cm⁻¹): 3374, 3000, 1706, 1708, 1609. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.25 (s, 1H, NH), 8.08 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.67–7.60 (m, 3H), 7.59–7.52 (m, 3H). ¹³C-NMR (101 MHz, DMSO-*d*₆): δ 155.36 (q, *J*_{C-C-F}= 37.0 Hz, <u>C</u>-CF₃), 154.81 (C=O), 149.36 (C, C=O), 137.96, 131.96, 131.48, 131.38, 130.16, 129.54 (q, *J*_{C-C-F}= 33.2 Hz, <u>C</u>-CF₃), 128.74, 128.63, 124.81, 122.48 (q, *J*_{C-F} = 271.8 Hz, C-<u>CF₃</u>), 121.65, 117.37, 114.29 (q, *J*_{C-F} = 279.0 Hz, C-<u>CF₃</u>). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -59.26 (s, 3F, CF₃), -71.41 (s, 3F, CF₃). Anal. Calcd for C₁₇H₁₀F₆N₄O₂ (416.28): C, 49.05; H, 2.42; N, 13.46. Found: C, 49.03; H, 2.49; N, 13.36%.

4-phenyl-1-(2,2,2-trifluoro-1-(p-tolylimino)ethyl)-1,2,4-triazolidine-3,5-dione (4g).

Cream solid. mp 281-287 °C. IR (KBr, cm⁻¹): 3401, 1790, 1758, 1701, 1623. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.98 (s, 1H, NH), 7.62–7.22 (m, 9H), 2.10 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 154.22 (C=O), 153.34 (C=O), 147.88 (q, *J*_{C-C-F} = 42.7 Hz, <u>C</u>-CF₃), 144.82, 134.26, 129.34, 129.26, 128.82, 126.68, 126.12, 126.06, 125.88 (2C), 121.51, 119.77, 114.20 (q, *J*_{C-F} = 271.1 Hz, C-<u>CF₃</u>), 21.00 (CH₃). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -74.01 (s, 3F, CF₃). Anal. Calcd for C₁₇H₁₃F₃N₄O₂ (362.31): C, 56.36; H, 3.62; N, 15.46. Found: C, 56.31; H, 3.45; N, 15.05%.

1-(1-(2,4-dimethylphenylimino)-2,2,2-trifluoroethyl)-4-phenyl-1,2,4-triazolidine-3,5-dione

(4h).

White solid. mp 110 °C. IR (KBr, cm⁻¹): 3374, 3000, 1703, 1700, 1609. ¹H-NMR (300 MHz, DMSO-*d*₆): δ 10.09 (s, 1H, NH), 7.90–6.47 (m, 8H), 2.39–1.99 (s, 6H, 2CH₃). ¹³C-NMR (75 MHz, DMSO-*d*₆): δ 151.81 (C=O), 151.50 (q, *J*_{C-C-F} = 32.4 Hz, <u>C</u>-CF₃), 150.03 (C=O), 144.52, 132.98, 131.83, 129.51, 128.70, 128.09, 127.83 (2C), 126.63 (3C), 122.03, 120.62 (q, *J*_{C-F} = 268.1 Hz, C-<u>CF₃</u>), 20.70 (CH₃), 18.72 (CH₃). ¹⁹F NMR (282.20 MHz, DMSO-*d*₆): δ -74.08(s, 3F, CF₃). Anal. Calcd for C₁₈H₁₅F₃N₄O₂ (376.34): C, 57.45; H, 4.02; N, 14.89. Found: C, 56.65; H, 4.05; N, 14.83%.

General procedure for the synthesis of (4i-4l) from 2, 3-dihydrophthalazine-1, 4-dione (2) A mixture of 2, 3-dihydrophthalazine-1, 4-dione 2 (1 mmol), Et₃N (3 mmol) and THF (5 mL) were stirred at r.t for 10 min and then a solution of aceteimidoyle chloride derivatives **3** (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at reflux. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and the resulting crude product was purified by plate chromatography on silica gel using hexane-ethyl acetate (6:2), producing the desired products **4i-1**, in 76-90% yield. 6-(trifluoromethyl)benzo[5,6][1,2,4]triazino[1,2-b]phthalazine-8,13-dione (4i). White solid. mp 128-134 °C. IR (KBr, cm⁻¹): 3022, 2877, 1714, 1667, 1624, 1600. ¹H-NMR

(400 MHz, DMSO-*d*₆): δ 7.19–6.87 (m, 4H), 8.24–7.87 (m, 4H). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 166.58 (C=O), 164.97 (C=O), 154.27 (q, *J*_{C-C-F} = 31.8 Hz, <u>C</u>-CF₃), 135.63, 133.85 (3C), 129.09 (2C), 126.95 (2C), 125.00, 124.97, 123.45, 116.47, 115.47 (q, *J*_{C-F} = 283.2 Hz, C-<u>CF₃</u>).

¹⁹F NMR (376.27 MHz, DMSO- d_6): δ -67.36 (s, 3F, CF₃). Anal. Calcd for C₁₆H₈F₃N₃O₂ (331.25): C, 58.01; H, 2.43; N, 12.69. Found: C, 57.87; H, 2.43; N, 12.58%. 2-fluoro-6-(trifluoromethyl)benzo[5,6][1,2,4]triazino[1,2-b]phthalazine-8,13-dione (4j). White solid. mp 146-147 °C. IR (KBr, cm⁻¹): 3020, 1701, 1654, 1611, 1586. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.25–8.17 (m, 1H), 8.09–7.93 (m, 3H), 7.30–7.20 (m, 2H), 6.94–6.85 (m, 1H). ¹³C-NMR (100 MHz, DMSO-d6): $\delta = 160.29(C=O)$, 159.29(C=O), 160.64 (d, $J_{C-F} = 251.8$ Hz, C-F), 157.42 (q, $J_{C-C-F} = 31.8$ Hz, C-CF₃), 134.75 (2C), 133.97 (2C), 131.64, 129.33(2C), 127.02 (2C), 123.53, 118.37 (q, $J_{C-F} = 269.9$ Hz, CF₃), 112.14 (d, $J_{C-C-F} = 25.8$ Hz), 105.29 (d, $J_{C-C-F} = 23.8$ Hz). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -67.23 (s, 3F, CF₃), -111.46 (m, 1F). Anal. Calcd for C₁₆H₇F₄N₃O₂ (349.24): C, 55.03; H, 2.02; N, 12.03. Found: C, 54.56; H, 2.34; N, 11.62%. 2-(2,2,2-trifluoro-1-(4-nitrophenylimino)ethyl)-2,3-dihydrophthalazine-1,4-dione (4k). White solid. mp 215-218 °C. IR (KBr, cm⁻¹): 3176, 3029, 2910, 1716, 1673, 1601. ¹H-NMR (400 MHz, DMSO- d_6): δ 12.41 (s, 1H, NH), 8.15 (d, J = 7.8 Hz, 1H), 8.07–7.89 (m, 5H), 7.28– 7.17 (m, 2H). ¹³C-NMR (100 MHz, DMSO- d_6): δ 166.49 (C=O), 155.28 (C=O), 145.87 (q, J_{C-C-F}) = 32.5 Hz, C-CF₃), 144.48, 142.88, 132.00 (2C), 131.26, 127.74, 126.87, 125.36 (2C), 125.27, 121.52(2C), 120.23 (q, J_{C-F}= 287 Hz, C-CF₃). ¹⁹F NMR (376.27 MHz, DMSO-d₆): δ -71.94 (s, 3F, CF₃). MS (m/z): Calcd for C₁₆H₉F₃N₄O₄ [M⁺] 377.0756, Found: 376.7000. 2-(2,2,2-trifluoro-1-((2,4,6-tribromophenyl)imino)ethyl)-2,3-dihydrophthalazine-1,4-dione (41). Bright brown solid. mp 220-226 °C. IR (KBr, cm⁻¹): 3029, 2909, 1733, 1666, 1600.¹H-NMR (400 MHz, DMSO- d_6): δ 12.54 (s, 1H, NH), 8.20 (d, J = 7.9 Hz, 1H), 8.05–7.79 (m, 5H). ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 159.33 (C=O), 148.01 (C=O), 145.08, 144.46, 135.72, 134.72, 133.94, 129.07, 126.92, 125.55, 125.34, 124.89, 123.66, 121.70, 121.51, 116.70 (q, J_{C-F}= 278) Hz, C-CF₃). ¹⁹F NMR (376.27 MHz, DMSO-*d*₆): δ -71.45 (s, 3F, CF₃). Anal. Calcd for C₁₆H₇Br₃F₃N₃O₂ (569.96): C, 33.72; H, 1.24; N, 7.37. Found: C, 33.66; H, 0.87; N, 7.14%. Acknowledgments

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<Figure>Scheme 1: Reactions of imidoyl chloride derivatives with urazole and phthalazine

<Figure>Scheme 2. Schematic presentation of the possible mechanism for products 4a-c and

4i.4l formation.

<Figure>Fig. 1: Biological active compounds base on urazole derivatives

<Figure>Figure 2. ¹H-NMR spectrum of compound 4a

<Figure **Figure 3**. ¹³C-NMR spectrum of compound **4a**

<Figure>Figure 4. HSQC spectrum of compound 4a

<Figure **Figure 5**. ¹⁹FNMR spectrum of compound **4a**

Tables

<Table>Table 1: Optimization of the solvent, temperature and base for reaction of urazole 1 with imidoyl chloride 2a

		F + 2a	F CF ₃ Base, solv	on	$O \qquad CF_3 \\ N \qquad N \\ N \qquad H \\ O \qquad F $
Entry	Base	solvent	Condition	Time (h)	Yields (%)
1	K ₂ CO ₃	DMF	r.t	24	0
2	K_2CO_3	DMF	reflux	18	0
3	NaH	THF	r.t	24	0
4	NaH	THF	60 °C	18	0
5	NaH	CH ₃ CN	r.t	24	40
6	NaH	CH ₃ CN	reflux	8	92

<Table>Table 2: Synthesis of products 4a-h





<Table>Table 3: Optimization of the solvent, temperature and base for reaction of phthalazine 2 with imidoyl chloride 3c



<Table>Table 4: Synthesis of products 4i-l



Entry	imidoyle	Products	Time (h)	Yield (%)
1	$ \begin{array}{c} $	O CF ₃ N N O 4i	10	88
2	$F \xrightarrow{K} F \xrightarrow{K} $	4j O CF ₃ N N N F	9	90
3	O_2N CF_3 3i	$ \begin{array}{c} $	12	76
4	$ \begin{array}{c} Br \\ F \\ Br \\ B$	O CF3 N NH Br G 4I	12	80

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