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Synthesis and SAR of phenylazoles, active against *Staphylococcus aureus* Newman

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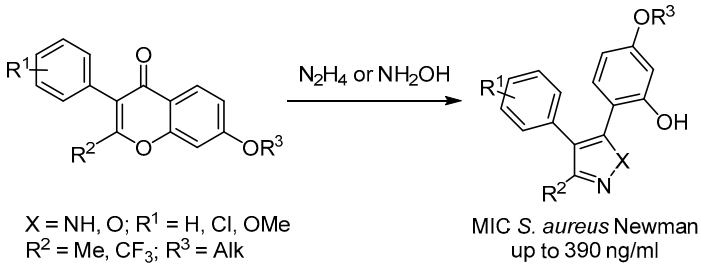


Series of new potent inhibitors of growth of *Staphylococcus aureus* Newman, based on 3,4-diphenylpyrazole and 4,5-diphenylisoxazole derivatives were discovered. Structures of interest were selectively modified to check their structure–activity relationship. Studies revealed the most essential groups in the molecule for the antimicrobial activity retention. Active compounds with good MIC range should contain both nonpolar aromatic residues and hydrogen bond donating groups. The best MIC results in selected cases were lower than 1 μg/ml.

Keywords: diphenylazole, isoflavone, isoxazole, pyrazole, antimicrobial activity, *Staphylococcus aureus* Newman.

The antibiotic resistance is one of the greatest health challenges requiring efficient solutions to prevent the increased number of lethal outcomes caused by bacterial infections.[1] The control of antimicrobial infections in hospitals is already complicated due to so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) which are resistant to virtually all marketed antibiotics.[2] The new antimicrobial drugs acting by yet unexploited mechanism are therefore urgently needed.

Recently Vo et al. reported 3,4-diarylpyrazole-based antibacterial compound series which was repurposed from compounds with anticancer activity acting as a heat shock protein 90 (HSP90) inhibitors (Fig. 1).[3] The antibacterial activity was linked to the inhibition of bacterial histidine kinases by binding to ATP-binding domain which share high similarity to the ATPase domain of eukaryotic HSP90. The representative compound **1** displayed micromolar inhibition of histidine kinases *C. crescentus* CckA and *Salmonella* PhoQ and medium activity against certain Gram negative and Gram positive bacterial strains. Structurally similar hit **2** with good potency against *S. aureus* was revealed in Wells lab by screening of compound libraries in antibacterial susceptibility tests. In this paper, we describe systematic investigation of SAR of diarylpyrazole-based compounds as well as scaffold hopping studies for the replacement of the pyrazole heterocycle with isoxazole.

The key intermediates for the synthesis of 3,4-diarylpyrazoles **8a**–**l** were isoflavones **7a**–**k** (Scheme 1).[4] These were synthesized from readily available resorcinol (**3**) and

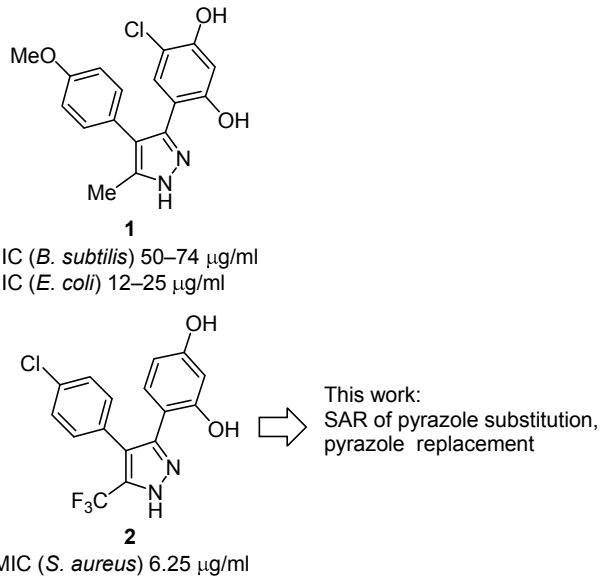
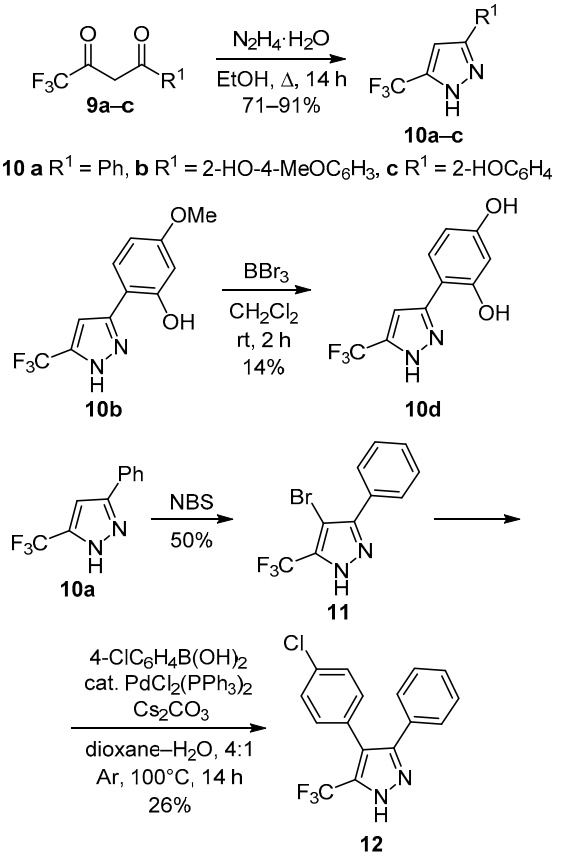


Figure 1. 3,4-Diarylpyrazoles with antibacterial activity.

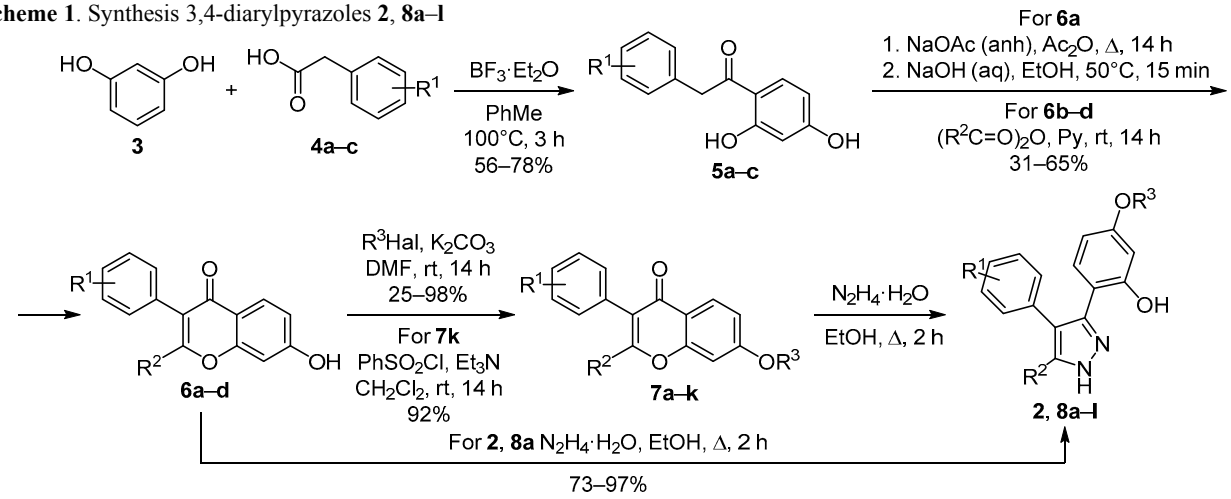
phenylacetic acid derivatives **4a**–**c** in two steps.[4b,5] The first step included Friedel–Crafts acylation of resorcinol (**3**), catalyzed by $BF_3 \cdot Et_2O$. The resulting acylresorcinols **5a**–**c** underwent condensation with acid anhydride followed by the cyclization to give isoflavones **6a**–**d**. *O*-Alkylation provided isoflavone derivatives **7a**–**k** which were condensed with hydrazine to provide the novel target compounds **8a**–**l**.

Synthesis of previously reported monoaryl pyrazoles **10a**,**c** and novel pyrazoles **10b**,**d** was achieved by the condensation of diketones **9a**–**c** with hydrazine (Scheme 2). One of the monoarylpyrazoles, compound **10a**, was further brominated to obtain bromo derivative **11** which was subjected to Suzuki–Miyaura coupling to provide the novel diarylpyrazole **12** (Scheme 2).

Scheme 2. Synthesis 3-aryl- and 3,4-diarylpyrazoles **10a–d**, **12**

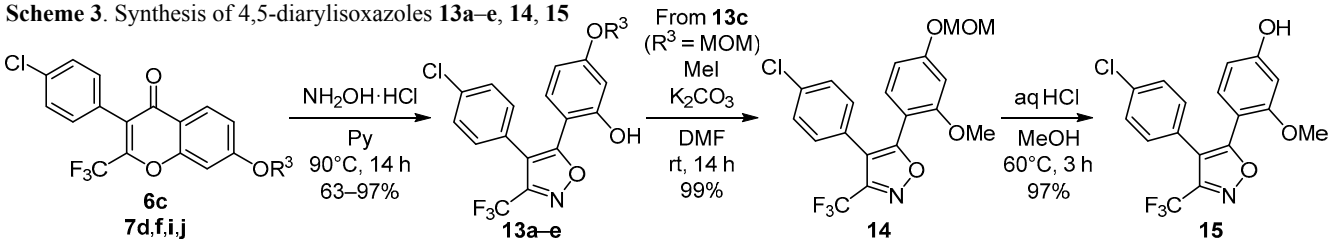


Scheme 1. Synthesis 3,4-diarylpyrazoles **2**, **8a–l**



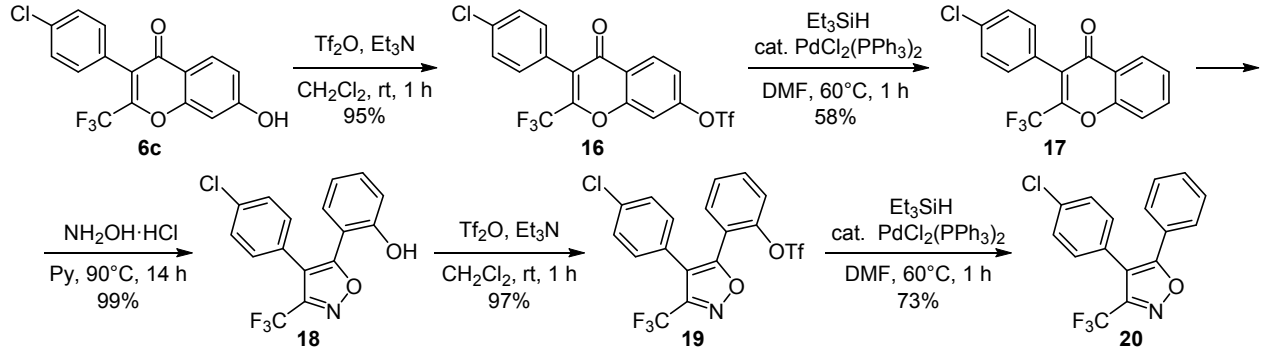
4, **5 a** R^1 = H, **b** R^1 = 4-Cl, **c** R^1 = 4-MeO
6 a R^1 = 4-Cl, R^2 = Me; **b** R^1 = H, R^2 = CF_3; **c** R^1 = 4-Cl, R^2 = CF_3; **d** R^1 = 4-MeO, R^2 = CF_3
7 a R^1 = 4-Cl, R^2 = CF_3, R^3 = Me; **b** R^1 = H, R^2 = CF_3, R^3 = Me; **c** R^1 = 4-MeO, R^2 = CF_3, R^3 = Me; **d** R^1 = 4-Cl, R^2 = CF_3, R^3 = Bn; **e** R^1 = H, R^2 = CF_3, R^3 = Bn; **f** R^1 = 4-Cl, R^2 = CF_3, R^3 = MOM; **g** R^1 = 4-Cl, R^2 = CF_3, R^3 = 2,6-$Cl_2C_6H_3CH_2$; **h** R^1 = 4-Cl, R^2 = CF_3, R^3 = 4-$BrC_6H_4CH_2$; **i** R^1 = 4-Cl, R^2 = CF_3, R^3 = *i*-Pr; **j** R^1 = 4-Cl, R^2 = CF_3, R^3 = $Me_2CH(CH_2)_2$; **k** R^1 = 4-Cl, R^2 = CF_3, R^3 = $PhSO_2$
2 R^1 = 4-Cl, R^2 = CF_3, R^3 = H; **8 a** R^1 = 4-Cl, R^2 = Me, R^3 = H; **b** R^1 = 4-Cl, R^2 = CF_3, R^3 = Me; **c** R^1 = H, R^2 = CF_3, R^3 = Me; **d** R^1 = 4-MeO, R^2 = CF_3, R^3 = Me; **e** R^1 = 4-Cl, R^2 = CF_3, R^3 = Bn; **f** R^1 = H, R^2 = CF_3, R^3 = Bn; **g** R^1 = 4-Cl, R^2 = CF_3, R^3 = MOM; **h** R^1 = 4-Cl, R^2 = CF_3, R^3 = 2,6-$Cl_2C_6H_3CH_2$; **i** R^1 = 4-Cl, R^2 = CF_3, R^3 = 4-$BrC_6H_4CH_2$; **j** R^1 = 4-Cl, R^2 = CF_3, R^3 = $PhSO_2$; **k** R^1 = 4-Cl, R^2 = CF_3, R^3 = *i*-Pr; **l** R^1 = 4-Cl, R^2 = CF_3, R^3 = $Me_2CH(CH_2)_2$

Scheme 3. Synthesis of 4,5-diarylisoxazoles **13a**–**e**, **14**, **15**



13 a R^3 = H, **b** R^3 = Bn, **c** R^3 = MOM, **d** R^3 = *i*-Pr, **e** R^3 = $(CH_2)_2CHMe_2$

Scheme 4. Synthesis of 4,5-diarylisoxazoles **18** and **20**

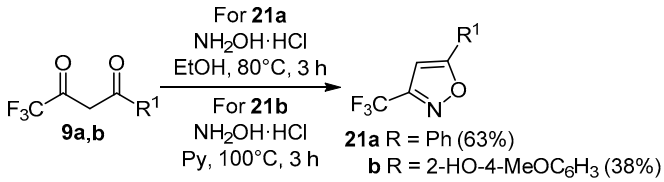


Novel isoxazole-based analogs **13a**–**e**, **14**, and **15** were obtained from isoflavone derivatives **6c**, **7d**,**f**,**i**,**j** (Scheme 3). Their reaction with hydroxylamine provided isoxazoles **13a**–**e**.[6] *O*-MOM-protected product **13c** was methylated at the free phenolic OH group, and the resulting derivative **14** was subjected to MOM deprotection in acid media to obtain isoxazole **15**.

Not previously described deoxygenated diarylisoxazole analogs **18** and **20** were prepared starting from isoflavone derivative **6c** (Scheme 4). Triflate formation with subsequent reduction has been tried. First, isoflavone **6c** transformed to triflate **16** in which the C–O bond was cleaved under Pd-catalyzed hydrogenolysis conditions using triethylsilane as hydrogen transfer reagent. The resulting isoflavone derivative **17** was converted to isoxazole **18**. It was then transformed to triflate **19** which was reduced to give product **20**.

Previously reported isoxazole **21a** and the novel isoxazole **21b** without a substituent in position 4 of heterocycle were prepared starting from diketones **9a**,**b** (Scheme 5).

Scheme 5. Synthesis of 4,5-diarylisoxazoles **21**

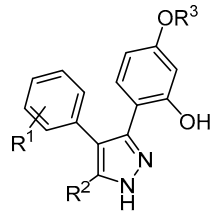


All synthesized compounds **8a**–**l**, **10a**–**d**, **12**, **13a**–**e**, **15**, **18**, **20**, **21a**,**b** were subjected to *in vitro* growth inhibiton tests of *Staphylococcus aureus* Newman.[7] The results of these tests are summarized in Tables 1–4.

Compound with methyl group as R^2 substituent (compound **8a**, Table 1) exhibited fourfold lower potency compared to the original hit **2**.

An improvement of the antibacterial potency was achieved by addition of methyl group as R^3 substituent (compound **8b**, Table 1). Replacement of 4-chlorophenyl with phenyl group as $R^1C_6H_4$ substituent (compound **8c**) or 4-methoxyphenyl group (compound **8d**) slightly decreased the antibacterial potency. However, *O*-benzyl group as R^3 substituent had a positive effect to antibacterial potency (compounds **8e**,**f**). Curiously, in the case of compounds **8e**,**f**, the difference in R^1 substitution did not affect MIC values which were retained around 1.56 μg/ml for both of

Table 1. Antibacterial activity of compounds **8a**–**l**

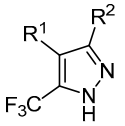


8a–l

Compound	R^1	R^2	R^3	MIC,* μg/ml
8a	4-Cl	Me	H	25
8b	4-Cl	CF_3	Me	3.12
8c	H	CF_3	Me	12.5
8d	4-OMe	CF_3	Me	12.5
8e	4-Cl	CF_3	Bn	1.56
8f	H	CF_3	Bn	1.56
8g	4-Cl	CF_3	MOM	3.12
8h	4-Cl	CF_3	2,6-Cl_2Bn	1.56
8i	4-Cl	CF_3	4-BrBn	1.56
8j	4-Cl	CF_3	$PhSO_2$	1.56
8k	4-Cl	CF_3	*i*-Pr	0.78
8l	4-Cl	CF_3	*i*-Amyl	<0.39

* *Staphylococcus aureus* Newman.

Table 2. Antibacterial activity of compounds **10a–d**, **12**



10a–d, **12**

Compound	R^1	R^2	MIC,* μg/ml
10a	H	Ph	50
10b	H	2-(HO)-4-(MeO)C_6H_3	25
10c	H	2-(HO)C_6H_4	125
10d	H	2,4-di(HO)C_6H_3	250
12	4-ClC_6H_5	Ph	1.56

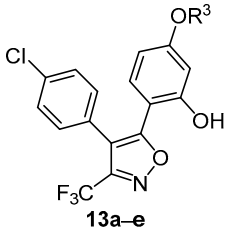
* *Staphylococcus aureus* Newman.

the compounds. MOM group as R^3 substituent (compound **8g**) only slightly increased activity in comparison with hit compound **2**. Substitution of benzyl group with 2,5-dichlorobenzyl (compound **8h**), 4-bromobenzyl (compound **8i**), and phenylsulfonyl (compound **8j**) group did not change the activity of the compounds in comparison with benzyl analog **8e**. The best antimicrobial activity in this series was exhibited by the compounds bearing lipophilic R^3 substituents such as isopropyl group (compound **8k**) and isoamyl group (compound **8l**).

Derivatives **10a–d** lacking substituents at position 4 of pyrazole ring showed significantly worse results in comparison with the hit compound **2** (Table 2). However, compound **12** with 4-chlorophenyl group as R^1 substituent and phenyl group as R^2 substituent exhibited activity four times higher than compound **2** (Table 2). These results point to the importance of the two aryl substituents at the pyrazole ring to ensure high antimicrobial potency. In addition, the high antimicrobial potency of compound **12** implies that hydroxyl groups at the phenyl group as the R^1 substituent are not essential.

Isoxazole analogs **13a–e** (Table 3) showed similar potency and SAR to their pyrazole peers **8e**,**g**,**k**,**l**, (Table 1). An interesting deviation was observed for isoxazoles **15**, **18**, **20**, and **21a**,**b** (Table 4). Compound **21a**, contrary to its pyrazole-based analog **10a**, completely lost activity against *S. aureus*. Compound **21b** possesses increased activity level in comparison with compound **10b**. Surprisingly, methylation of *o*-hydroxy group in R^2 substituent (compound **15**, Table 4) did not affect MIC value – it was retained at 3.12 μg/ml. Finally, compound **20** totally lost the antimicrobial potency (Table 4) in comparison with pyrazole derivative **12** having the same substitution pattern (Table 2).

Table 3. Activity of isoxazole-based compounds **13a–e**

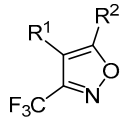


13a–e

Compound	R^3	MIC,* μg/ml
13a	H	3.12
13b	Bn	0.78
13c	MOM	3.12
13d	*i*-Pr	0.78
13e	*i*-Amyl	<0.39

* *Staphylococcus aureus* Newman.

Table 4. Activity of simplified isoxazole-based compounds **15**, **18**, **20**, **21a**,**b**



15, **18**, **20**, **21a**,**b**

Compound	R^1	R^2	MIC,* μg/ml
21a	H	Ph	Inactive
21b	H	2-(HO)-4-(MeO)C_6H_3	6.25
15	4-ClC_6H_5	2-(MeO)-4-(HO)C_6H_3	3.12
18	4-ClC_6H_5	2-(HO)C_6H_4	3.12
20	4-ClC_6H_5	Ph	Inactive

* *Staphylococcus aureus* Newman.

The most efficient compounds, such as **8k**,**l** were exhibiting activity level against *Staphylococcus aureus* Newman comparable with well-known antibiotics such as ampicillin (MIC 1.0 μg/ml), ciprofloxacin (MIC 0.5 μg/ml), and vancomycin (MIC 1.0 μg/ml).

The SAR of the compounds provides the directions for further structural improvements to achieve more potent phenylazole-based antimicrobials. Thus, introduction of the lipophilic groups at position 5 of phenolic ring of the molecule increased the potency of compounds **8e**,**k**. Further increase of lipophilicity in this position could increase the potency. Additionally, further work should explore another suitable 5-membered cycles such as imidazole, 1,2,3-triazole, or isothiazole as scaffolds to improve the potency of the compounds. Nevertheless, the SAR of the pairs of compounds **12** and **20**, or **18** and **20** implies that at least one NH or OH group should be retained in the inhibitor to preserve its potency.

Our investigation of growth inhibition of *S. aureus* Newman by 3,4-diphenylpyrazole and 4,5-diphenylisoxazole derivatives lead to several very potent antibacterial compounds. The most potent growth inhibitors were pyrazole-based compounds **8k**,**l** and their isoxazole analogs **13d**,**e** with MIC <1 μg/ml. The studies revealed the most crucial elements for their antimicrobial activity. The structure should contain at least one hydrogen bond donor either in heterocycle or at aryl groups. Pyrazole replacement with isoxazole in most cases did not affect activity, however, several differences were found. For example, both aryl groups were needed at positions 3 and 4 for pyrazole-based compounds to exhibit high potency, however, relatively potent compound **21b** was found in

isoxazole series lacking aryl group at position 3 of isoxazole. The mechanism of action for pyrazole- and isoxazole-based *S. aureus* growth inhibitors needs further investigation.

Experimental

^{1}H NMR spectra were recorded on 300, 400, or 600 MHz Bruker spectrometers. ^{13}C and ^{19}F NMR spectra were recorded on 400 (101 and 376 MHz, respectively) or 600 MHz Bruker spectrometers (151 and 564 MHz, respectively) using the residual solvent peak as internal reference ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei; $(CD_3)_2CO$: 2.05 ppm for ^{1}H nuclei and 29.8 and 206.3 ppm for ^{13}C nuclei). HRMS were determined on a Waters Synapt G2-Si hybrid quadrupole time-of-flight (TOF) mass spectrometer equipped with an electron spray ion source (ESI). Melting points were detected with an OptiMelt MPA100 melting point apparatus, with a heating rate of 3°C/min. When necessary, compounds were purified by crystallization or by column chromatography on silica gel (petroleum ether – EtOAc gradient).

Reagents were purchased from commercial sources and used as received. Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of moisture.

Synthesis of 1-(2,4-dihydroxyphenyl)-2-phenylethan-1-ones 5a–c (General method). Procedure described in literature have been used.[8] $BF_3{\cdot}Et_2O$ (15.46 ml, 17.47 g, 123 mmol) was added slowly to a solution of resorcinol (**3**) (4.52 g, 41 mmol) and phenylacetic acid **4a–c** (41 mmol) in anhydrous PhMe (120 ml). Resulting solution was heated at 100°C for 3 h and cooled down to room temperature. The mixture was poured into saturated NaOAc solution (300 ml) and then partitioned with EtOAc (300 ml). The EtOAc extract was washed with brine (2×200 ml). The extract was dried over Na_2SO_4 and concentrated *in vacuo*. Thus obtained crude product was triturated with PhMe or purified by column chromatography on silica gel using gradient EtOAc in petroleum ether.

1-(2,4-Dihydroxyphenyl)-2-phenylethan-1-one (5a) was synthesized from phenylacetic acid (**4a**) (1.1 g). Yield 1.23 g (66%), yellowish sticky oil. Spectral data was in accordance with the previously reported.[9]

2-(4-Chlorophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (5b) was synthesized from 4-chlorophenylacetic acid (**4b**) (7.0 g). Yield 6.0 g (56%), slightly pink solid. Spectral data was in accordance with the previously reported.[10]

1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one (5c) was synthesized from 4-methoxyphenylacetic acid (**4c**) (350 mg). Yield 640 mg (78%), yellowish solid. Spectral data was in accordance with the previously reported.[11]

3-(4-Chlorophenyl)-7-hydroxy-2-methyl-4*H*-chromen-4-one (6a). Procedure, described in literature, have been used.[12] 2-(4-Chlorophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (**5b**) (700 mg, 2.7 mmol) and anhydrous NaOAc (437 mg, 5.4 mmol) were dissolved in Ac_2O (4 ml, 42.6 mmol). The mixture was refluxed for 14 h, cooled, and poured into H_2O. The precipitate was filtered off, dried, and recrystallized from EtOH to obtain acylated intermediate as a slightly yellow solid (594 mg, 1.8 mmol). This material was suspended in EtOH (5 ml), and aqueous NaOH (86.7 mg, 2.2 mmol) was added thereto. After heating at 50°C for 15 min, solvent was distilled off under reduced pressure, residue was dissolved in H_2O and acidified by 1 M HCl. Formed precipitate was filtered off and dried. Yield 496 mg (65% over 2 steps), white-beige solid. Spectral data was in accordance with the previously reported.[12]

Synthesis of 7-hydroxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-ones 6b–d (General method). Procedure, described in literature, have been used.[13] Trifluoroacetic acid anhydride (9 ml, 13.6 g, 64.8 mmol) was added dropwise to an ice-cooled solution of deoxybenzoin (16.2 mmol) in pyridine (20 ml). The resulting solution was stirred for 14 h at room temperature. Reaction mixture was diluted with EtOAc (200 ml), washed with 1 M HCl (3×150 ml), brine (150 ml), and dried over anhydrous Na_2SO_4, followed by evaporation *in vacuo*. Crude product was triturated with EtOH–H_2O, 1:1 (for compounds **6b**,**c**) or EtOAc – petroleum ether, 1:3 (for compound **6d**) mixture.

7-Hydroxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (6b) was synthesized from compound **5a** (570 mg). Yield 497 mg (65%), white-beige solid. Spectral data was in accordance with the previously reported.[14]

3-(4-Chlorophenyl)-7-hydroxy-2-(trifluoromethyl)-4*H*-chromen-4-one (6c) was synthesized from compound **5b** (4.25 g). Yield 3.47 g (63%), white-yellow solid, mp 248–250°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.18 (1H, s, OH); 7.93 (1H, d, *J* = 8.8, H-5); 7.52 (2H, d, *J* = 8.5 C_6H_4Cl); 7.31 (2H, d, *J* = 8.5, C_6H_4Cl); 7.02 (1H, dd, *J* = 8.8, *J* = 2.2, H-8); 6.96 (1H, d, *J* = 2.2, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 175.1; 164.1; 156.6; 146.8 (q, *J* = 35.5); 133.6; 131.9; 128.6; 128.2; 127.6; 124.0; 119.4 (q, *J* = 276.4); 116.6; 115.5; 102.4. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.86. Found, *m*/*z*: 341.0198 $[M+H]^+$. $C_{16}H_9ClF_3O_3$. Calculated, *m*/*z*: 341.0192.

7-Hydroxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (6d) was synthesized from compound **5c** (640 mg). Yield 258 mg (31%), light-brown solid. Spectral data was in accordance with the previously reported.[13]

Synthesis of 7-(alkyloxy)-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-ones 7a–j (General method). Alkyl chloride, iodide, or bromide (0.6 mmol) was added to a stirred solution of compound **6b–d** (0.45 mmol) and K_2CO_3 (1 mmol) in DMF (3 ml). The resulting solution was stirred for 14 h at room temperature. Reaction mixture was diluted with EtOAc (50 ml), washed with brine (3×50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was crystallized from EtOH.

3-(4-Chlorophenyl)-7-methoxy-2-(trifluoromethyl)-4*H*-chromen-4-one (7a) was synthesized from compound **6c** (300 mg), using MeI as alkylating agent. Yield 258 mg (83%), white solid, mp 162–164°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.12 (1H, d, *J* = 8.9,

H-5); 7.42 (2H, d, *J* = 8.5, C_6H_4Cl); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.05 (1H, dd, *J* = 8.9, *J* = 2.4, H-8); 6.95 (1H, d, *J* = 2.3, H-6); 3.95 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 165.3; 157.1; 148.3 (q, *J* = 36.5); 135.1; 131.4; 128.7; 128.0; 127.7; 124.6; 119.4 (q, *J* = 276.7); 117.1; 116.2; 100.3; 56.2. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.56. Found, *m*/*z*: 355.0360 $[M+H]^+$. $C_{17}H_{11}ClF_3O_3$. Calculated, *m*/*z*: 355.0349.

7-Methoxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (7b) was synthesized from compound **6b** (200 mg) using MeI as alkylating agent. Yield 98 mg (47%), yellowish solid. Spectral data was in accordance with the previously reported.[15]

7-Methoxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7c) was synthesized from compound **6d** (138 mg) using MeI as alkylating agent. Yield 114 mg (79%), beige solid, mp 135–138°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.13 (1H, d, *J* = 8.9, H-5); 7.19 (2H, d, *J* = 8.7, $C_6\underline{H}_4OMe$); 7.03 (1H, dd, *J* = 8.9, *J* = 2.4, H-8); 6.97 (2H, d, *J* = 8.8, H Ar, $C_6\underline{H}_4OMe$); 6.94 (1H, d, *J* = 2.4, H-6); 3.95 (3H, s, OCH_3); 3.85 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 176.5; 165.1; 160.1; 157.1; 148.1 (q, *J* = 35.6); 131.2; 128.0; 125.5; 121.2; 119.6 (q, *J* = 275.8); 117.3; 116.0, 113.9, 100.2, 56.2, 55.4. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.58. Found, *m*/*z*: 351.0857 $[M+H]^+$. $C_{18}H_{14}F_3O_4$. Calculated, *m*/*z*: 351.0844.

7-(Benzyloxy)-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7d) was synthesized from compound **6c** (500 mg) using BnBr as alkylating agent. Yield 585 mg (92%), white solid, mp 160–162°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.14 (1H, d, *J* = 8.9, H-5); 7.49–7.35 (7H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.13 (1H, dd, *J* = 8.9, *J* = 2.4, H-8); 7.03 (1H, d, *J* = 2.3, H-6); 5.20 (2H, s, $OC\underline{H}_2Ph$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 164.3; 156.9; 148.3 (q, *J* = 36.2); 135.4; 135.1; 131.4; 129.0; 128.7 (2C); 128.1; 127.7; 127.6; 124.6; 119.4 (q, *J* = 276.8); 117.3; 116.7; 101.4; 70.9. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.74. Found, *m*/*z*: 431.0672 $[M+H]^+$. $C_{23}H_{15}ClF_3O_3$. Calculated, *m*/*z*: 431.0662.

7-(Benzyloxy)-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (7e) was synthesized from compound **6b** (180 mg) using BnBr as alkylating agent. Yield 60 mg (26%), white solid, mp 123–125°C. ^1H NMR spectrum (400 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 8.02 (1H, d, *J* = 9.1, H-5); 7.53–7.49 (2H, m, H Ph); 7.44–7.37 (5H, m, H Ph); 7.37–7.32 (1H, m, H Ph); 7.32–7.27 (2H, m, H Ph); 7.26 (1H, d, *J* = 2.2, H-8); 7.20 (1H, dd, *J* = 8.9, *J* = 2.4, H-6); 5.34 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 176.1; 165.1; 157.8; 148.3 (q, *J* = 35.7); 137.1; 130.9 (q, *J* = 1.4); 130.7; 129.5; 129.3; 129.1; 128.7; 128.6; 128.2; 126.6; 120.6 (q, *J* = 275.6); 118.1; 117.3; 102.3; 71.5. ^{19}F NMR spectrum (376 MHz, $(CD_3)_2CO$), δ, ppm: –64.31. Found, *m*/*z*: 397.1057 $[M+H]^+$. $C_{23}H_{16}F_3O_3$. Calculated, *m*/*z*: 397.1052.

3-(4-Chlorophenyl)-7-(methoxymethoxy)-2-(trifluoromethyl)-4*H*-chromen-4-one (7f) was synthesized from compound **6c** (400 mg) using MOMCl as alkylating agent. Yield 262 mg (58%), off-white solid, mp 125–127°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.14 (1H, d, *J* = 8.9, H-5); 7.42 (2H, d, *J* = 8.5, C_6H_4Cl); 7.23–7.17 (3H, m, H Ar); 7.13 (1H, dd, *J* = 8.9, *J* = 2.3, H-6); 5.31 (2H, s, $OC\underline{H}_2OCH_3$), 3.52 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 176.0; 162.7; 156.7; 148.5 (q, *J* = 36.2); 135.2; 131.4; 128.7; 128.0; 127.7; 124.6; 119.4 (q, *J* = 276.4); 117.9; 117.0; 103.3; 94.6; 56.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.57. Found, *m*/*z*: 385.0465 $[M+H]^+$. $C_{18}H_{13}ClF_3O_4$. Calculated, *m*/*z*: 385.0454.

3-(4-Chlorophenyl)-7-[(2,6-dichlorobenzyl)oxy]-2-(trifluoromethyl)-4*H*-chromen-4-one (7g) was synthesized from compound **6c** (150 mg) using 2-(bromomethyl)-1,3-dichlorobenzene as alkylating agent. Yield 172 mg (78%), light-yellow solid, mp 196–197°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.16 (1H, d, *J* = 9.4, H-5); 7.46–7.39 (4H, m, H Ar); 7.31 (1H, dd, *J* = 8.8, *J* = 7.2, H Ar); 7.21 (2H, d, *J* = 8.4, C_6H_4Cl); 7.16–7.10 (2H, m, H Ar); 5.42 (2H, s, $OC\underline{H}_2C_6H_3Cl_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 164.3; 156.9; 137.2; 135.2; 131.4; 131.2; 130.9; 128.8; 128.7; 128.1; 127.7; 124.7; 119.4 (d, *J* = 276.6) 117.5; 116.6; 101.3; 100.1; 65.9. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.55. Found, *m*/*z*: 498.9877 $[M+H]^+$. $C_{23}H_{13}Cl_3F_3O_3$. Calculated, *m*/*z*: 498.9882.

7-[(4-Bromobenzyl)oxy]-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7h) was synthesized from compound **6c** (150 mg) using 1-bromo-4-(bromomethyl)-benzene as alkylating agent. Yield 114 mg (51%), pink solid, mp 153–155°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.14 (1H, d, *J* = 8.9, H-5); 7.56 (2H, d, *J* = 8.4, C_6H_4Br); 7.42 (2H, d, *J* = 8.5, C_6H_4Cl); 7.33 (2H, d, *J* = 8.4, C_6H_4Br); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.11 (1H, dd, *J* = 8.9, *J* = 2.4, H-8); 7.00 (1H, d, *J* = 2.3, H-6); 5.15 (2H, s, $OC\underline{H}_2C_6H_4Br$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 164.0; 156.9; 148.4 (q, *J* = 36.0); 135.2; 134.4; 132.2; 131.3; 129.2; 128.7; 128.2; 127.6; 124.7; 122.7; 120.8; 119.4 (q, *J* = 276.7); 116.6; 101.4; 70.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.53. Found, *m*/*z*: 508.9775 $[M+H]^+$. $C_{23}H_{14}BrClF_3O_3$. Calculated, *m*/*z*: 508.9767.

3-(4-Chlorophenyl)-7-isopropoxy-2-(trifluoromethyl)-4*H*-chromen-4-one (7i) was synthesized from compound **6c** (250 mg) using *i*-PrI as alkylating agent. Yield 275 mg (98%), yellowish solid, mp 128–130°C. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.11 (1H, d, *J* = 8.9, H-5); 7.42 (2H, d, *J* = 8.6, C_6H_4Cl); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.00 (1H, dd, *J* = 8.9, *J* = 2.3, H-8); 6.91 (1H, d, *J* = 2.3, H-6); 4.70 (1H, hept, *J* = 5.8, $OC\underline{H}(CH_3)_2$), 1.43 (6H, d, *J* = 6.1, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 163.8; 157.1; 148.2 (q, *J* = 36.3); 135.1; 131.4; 128.7; 128.0; 127.8; 124.6; 119.5 (q, *J* = 276.7); 117.2; 116.8; 101.5; 71.3; 21.9. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.58. Found, *m*/*z*: 383.0656 $[M+H]^+$. $C_{19}H_{15}ClF_3O_3$. Calculated, *m*/*z*: 383.0662.

3-(4-Chlorophenyl)-7-(isopentyloxy)-2-(trifluoromethyl)-4*H*-chromen-4-one (7j) was synthesized from compound **6c** (250 mg) using isoamyl bromide as alkylating agent.

Yield 297 mg (98%), yellow solid, mp 80–82°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.11 (1H, d, *J* = 8.9, H-5); 7.42 (2H, d, *J* = 8.5, C_6H_4Cl); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.03 (1H, dd, *J* = 8.9, *J* = 2.3, H-8); 6.94 (1H, d, *J* = 2.3, H-6); 4.12 (2H, t, *J* = 6.6, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.95–1.80 (1H, m, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.77 (2H, t, *J* = 6.5, $OCH_2C\underline{H}_2CH(CH_3)_2$); 1.00 (6H, d, *J* = 6.5, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 164.8; 157.1; 148.3 (q, *J* = 36.3); 135.1; 131.4; 128.6; 127.9; 124.6; 119.5 (q, *J* = 276.7); 116.9; 116.6; 110.2; 100.7; 67.6; 37.7; 25.2; 22.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.59. Found, *m*/*z*: 411.0981 $[M+H]^+$. $C_{21}H_{19}ClF_3O_3$. Calculated, *m*/*z*: 411.0975.

3-(4-Chlorophenyl)-4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl benzenesulfonate (7k). Phenylsulfonyl chloride (233 mg, 1.33 mmol) was added to a stirred solution of compound **6c** (300 mg, 0.88 mmol) and Et_3N (245 μl, 1.76 mmol) in CH_2Cl_2 (5 ml). Resulting solution was stirred for 14 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (15 ml), washed with brine (3×50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was purified by silica gel column chromatography, using gradient from 5 to 20% EtOAc in petroleum ether. Yield 390 mg (92%), brown oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.16 (1H, d, *J* = 8.8, H-5); 7.91 (2H, d, *J* = 7.3, H Ar); 7.74 (1H, t, *J* = 7.5, H Ar); 7.60 (2H, t, *J* = 7.9, H Ar); 7.49–7.35 (3H, m, H Ar); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 7.07 (1H, dd, *J* = 8.8, *J* = 2.2, H-6). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 155.4; 154.1; 149.1 (q, *J* = 36.6); 135.5; 135.1; 135.0; 131.2; 129.7; 128.8; 128.6; 128.5; 127.0; 125.0; 121.9; 121.0; 119.2 (q, *J* = 277.2); 112.4. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.56. Found, *m*/*z*: 481.0128 $[M+H]^+$. $C_{22}H_{13}ClF_3O_5S$. Calculated, *m*/*z*: 481.0124.

Synthesis of pyrazoles 2, 8a–l (General method). Hydrazine hydrate (1.3 ml, 27.6 mmol) was added to a stirred solution of compound **6a**,**c**, **7a**–**k** (0.67 mmol) in EtOH (5 ml). Resulting solution was stirred for 2 h at reflux. Reaction mixture was evaporated to dryness and triturated with cold H_2O.

4-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol (2) was synthesized from compound **6c** (258 mg). Yield 208 mg (77%), white solid. Spectral data was in accordance with the previously reported.[16]

4-[4-(4-Chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl]-benzene-1,3-diol (8a) was synthesized from compound **6a** (183 mg). Yield 158 mg (94%), white solid, mp 231–234°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.52 (1H, s, NH); 10.58 (1H, s, OH), 9.38 (1H, s, OH); 7.37–7.20 (4H, m, C_6H_4Cl); 6.76 (1H, d, *J* = 7.8, H Ar); 6.29–6.11 (2H, m, H Ar); 2.19 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 157.9; 157.0; 147.0; 137.6; 131.4; 130.3; 128.8; 128.5; 128.1; 115.1; 109.7; 106.3; 102.8; 12.9. Found, *m*/*z*: 301.0752 $[M+H]^+$. $C_{16}H_{14}ClN_2O_2$. Calculated, *m*/*z*: 301.0744.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-methoxyphenol (8b) was synthesized from compound **7a** (600 mg). Yield 600 mg (96%), white-beige solid, mp 178–180°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.39 (2H, d, *J* = 8.4, C_6H_4Cl); 7.19 (2H, d, *J* = 8.4, C_6H_4Cl); 6.85 (1H, d, *J* = 8.5, H-5); 6.42 (1H, d, *J* = 2.4, H-2); 6.29 (1H, dd, *J* = 8.5, *J* = 2.4, H-6); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 161.2; 156.8; 139.8; 138.1 (q, *J* = 36.0); 132.2; 131.9; 131.4; 130.6; 128.4; 122.2 (q, *J* = 269.2); 116.9; 107.8; 105.0; 101.5; 55.2. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.88. Found, *m*/*z*: 369.0628 $[M+H]^+$. $C_{17}H_{13}ClF_3N_2O_2$. Calculated, *m*/*z*: 369.0618.

5-Methoxy-2-[4-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8c) was synthesized from compound **7b** (91 mg). Yield 82 mg (86%), white solid, mp 145–147°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.35–7.24 (3H, m, H Ar); 7.21–7.14 (2H, m, H Ar); 6.85 (1H, d, *J* = 8.5, H-3); 6.45 (1H, d, *J* = 2.5, H-6); 6.31 (1H, dd, *J* = 8.6, *J* = 2.5, H-4); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.9; 156.7; 139.3; 138.1 (q, *J* = 34.8); 131.8; 131.5; 129.6; 128.1; 127.1; 122.2 (q, *J* = 269.2); 118.0; 108.0; 104.7; 101.3; 55.0. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.80. Found, *m*/*z*: 335.1021 $[M+H]^+$. $C_{17}H_{14}F_3N_2O_2$. Calculated, *m*/*z*: 335.1007.

5-Methoxy-2-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8d) was synthesized from compound **7c** (102 mg). Yield 77 mg (73%), beige powder, mp 75–79°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.09 (2H, d, *J* = 8.2, $C_6\underline{H}_4OMe$); 6.87 (3H, t, *J* = 8.2, H Ar); 6.45 (1H, s, H-6); 6.32 (1H, d, *J* = 9.9, H-4); 3.73 (3H, s, OCH_3); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.7; 158.3; 156.7; 139.2; 138.1 (q, *J* = 36.0); 131.7; 130.7; 123.5; 122.3 (q, *J* = 270.1); 117.6; 113.6; 108.2; 104.7; 101.3; 55.0 (q, *J* = 4.4). ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m*/*z*: 365.1121 $[M+H]^+$. $C_{18}H_{16}F_3N_2O_3$. Calculated, *m*/*z*: 365.1113.

5-(Benzyloxy)-2-[4-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8e) was synthesized from compound **7d** (289 mg). Yield 274 mg (92%), white solid, mp 78–81°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.46–7.28 (7H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 6.89 (1H, d, *J* = 8.5, H-3); 6.50 (1H, d, *J* = 2.3, H-6); 6.43 (1H, dd, *J* = 8.5, *J* = 2.3, H-4); 5.03 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.2; 156.7; 139.8; 138.2 (q, *J* = 34.7); 136.9; 132.2; 131.9; 131.4; 130.6; 128.6; 128.4; 128.1; 127.9; 122.2 (q, *J* = 269.2); 117.0; 108.0; 105.8; 102.4; 69.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.59. Found, *m*/*z*: 445.0934 $[M+H]^+$. $C_{23}H_{17}ClF_3N_2O_2$. Calculated, *m*/*z*: 445.0931.

5-(Benzyloxy)-2-[4-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8f) was synthesized from compound **7e** (48 mg). Yield 46 mg (92%), white solid, mp 84–88°C. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 7.46–7.26 (9H, m, H Ar, $OCH_2C_6\underline{H}_5$); 6.90 (1H, d, *J* = 8.6, H-3); 6.63 (1H, d, *J* = 2.4, H-6); 6.40 (1H, dd, *J* = 8.6, *J* = 2.4, H-4), 5.06 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 161.4; 157.3; 140.3; 138.1; 132.9; 132.2; 131.1; 129.3; 129.1; 128.7; 128.5; 128.2; 122.3 (q, *J* = 268.8); 119.0; 109.4; 107.0; 103.5; 70.5. ^{19}F NMR spectrum (376 MHz, $(CD_3)_2CO$), δ, ppm: –59.66.

Found, *m*/*z*: 411.1344 $[M+H]^+$. $C_{23}H_{18}F_3N_2O_2$. Calculated, *m*/*z*: 411.1320.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-(methoxymethoxy)phenol (8g) was synthesized from compound **7f** (136 mg). Yield 117 mg (83%), white-gray powder, mp 190–193°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.00 (2H, br. s, NH, OH); 7.39 (2H, d, *J* = 8.3, C_6H_4Cl); 7.19 (2H, d, *J* = 8.3, C_6H_4Cl); 6.91 (1H, d, *J* = 8.5, H-3); 6.57 (1H, d, *J* = 2.0, H-6); 6.43 (1H, dd, *J* = 8.5, *J* = 2.0, H-4); 5.13 (2H, s, $OC\underline{H}_2OCH_3$); 3.35 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 158.5; 156.6; 139.5; 138.1 (q, *J* = 34.3); 132.0; 131.7; 131.3; 130.5; 128.3; 122.1 (q, *J* = 269.0); 116.9; 108.6; 106.9; 103.3; 93.6; 55.6. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m*/*z*: 399.0735 $[M+H]^+$. $C_{18}H_{15}ClF_3N_2O_3$. Calculated, *m*/*z*: 399.0723.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-[(2,6-dichlorobenzyl)oxy]phenol (8h) was synthesized from compound **7g** (161 mg). Yield 138 mg (83%), white solid, mp 92–94°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.60–7.52 (2H, m, H Ar); 7.46 (1H, dd, *J* = 8.9, *J* = 7.1, H Ar); 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.21 (2H, d, *J* = 8.4, C_6H_4Cl); 6.95 (1H, d, *J* = 8.3, H-3); 6.59–6.47 (2H, m, H Ar); 5.16 (2H, s, $OC\underline{H}_2C_6H_3Cl_2$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.3; 156.8; 139.8; 138.3 (q, *J* = 34.4); 136.2; 132.2; 132.1; 131.8; 131.6; 131.5; 130.6; 128.9; 128.4; 122.2 (q, *J* = 269.1); 117.0; 108.6; 105.3; 102.3; 65.0. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.83. Found, *m*/*z*: 513.0157 $[M+H]^+$. $C_{23}H_{15}Cl_3F_3N_2O_2$. Calculated, *m*/*z*: 513.0151.

5-[(4-Bromobenzyl)oxy]-2-[4-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8i) was synthesized from compound **7h** (114 mg). Yield 93 mg (79%), beige solid, mp 83–85°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.58 (2H, d, *J* = 8.4, C_6H_4Br); 7.44–7.30 (4H, m, C_6H_4Cl, C_6H_4Br); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 6.86 (1H, d, *J* = 8.5, H-3); 6.47 (1H, d, *J* = 2.4, H-6); 6.37 (1H, dd, *J* = 8.6, *J* = 2.4, H-4); 5.01 (2H, s, $OC\underline{H}_2C_6H_4Br$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.0; 156.8; 139.7; 138.2 (q, *J* = 33.3); 136.4; 132.2; 131.9; 131.5; 131.4; 130.6; 130.0; 128.4; 122.2 (q, *J* = 269.1); 121.1; 117.0; 108.2; 105.7; 102.4; 68.5. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m*/*z*: 525.0023 $[M+H]^+$. $C_{23}H_{16}BrClF_3N_2O_2$. Calculated, *m*/*z*: 525.0040.

4-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-3-hydroxyphenyl benzenesulfonate (8j) was synthesized from compound **7k** (250 mg). Yield 228 mg (89%), beige solid, mp 193–196°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.87–7.79 (3H, m, H Ar); 7.66 (2H, t, *J* = 7.8, H Ar); 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.15 (2H, d, *J* = 8.4, C_6H_4Cl); 6.90 (1H, d, *J* = 8.5, H-2); 6.51 (1H, d, *J* = 2.4, H-5); 6.28 (1H, dd, *J* = 8.5, *J* = 2.4, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 158.0 (d, *J* = 16.5); 149.4 (d, *J* = 4.1); 140.3 (d, *J* = 14.2); 138.2 (d, *J* = 34.3); 134.9; 134.4; 132.0; 131.4; 131.0 (d, *J* = 8.6); 130.1 (d, *J* = 13.6); 129.8; 128.3; 128.1; 122.4 (d, *J* = 272.6); 116.3 (d, *J* = 9.0); 115.3 (d, *J* = 4.6); 111.2 (d, *J* = 9.9); 109.6. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.30. Found, *m*/*z*: 495.0407 $[M+H]^+$. $C_{22}H_{15}ClF_3N_2O_4S$. Calculated, *m*/*z*: 495.0393

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-isopropoxyphenol (8k) was synthesized from compound **7i** (130 mg). Yield 129 mg (95%), white solid, mp 176–178°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.38 (2H, d, *J* = 8.1, C_6H_4Cl); 7.18 (2H, d, *J* = 8.1, C_6H_4Cl); 6.86 (1H, d, *J* = 8.5, H-3); 6.41 (1H, s, H-6); 6.32 (1H, d, *J* = 8.4, H-4); 4.49 (1H, sept, *J* = 5.7, $OC\underline{H}(CH_3)_2$); 1.22 (6H, d, *J* = 5.9, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (151 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 159.2; 156.8; 139.8; 138.0 (q, *J* = 34.6); 131.9; 131.6; 131.3; 130.7; 128.2; 122.2 (q, *J* = 269.0); 116.6; 107.4; 106.1; 102.8; 69.2; 21.8. ^{19}F NMR spectrum (564 MHz, $CDCl_3$), δ, ppm: –53.02. Found, *m*/*z*: 397.0932 $[M+H]^+$. $C_{19}H_{17}ClF_3N_2O_2$. Calculated, *m*/*z*: 397.0931.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-(isopentyloxy)phenol (8l) was synthesized from compound **7j** (140 mg). Yield 141 mg (97%), light-yellow solid, mp 73–75°C. ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.38 (2H, d, *J* = 8.4, C_6H_4Cl); 7.24 (2H, d, *J* = 8.3, C_6H_4Cl); 6.82 (1H, d, *J* = 8.8, H-3); 6.49 (1H, s, H-6); 6.27 (1H, dd, *J* = 8.8, *J* = 1.9, H-4); 3.92 (2H, t, *J* = 6.7, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.77 (1H, sept, *J* = 6.7, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.63 (2H, q, *J* = 6.7, $OCH_2C\underline{H}_2CH(CH_3)_2$); 0.93 (6H, d, *J* = 6.6, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.6; 156.7; 139.8; 138.3 (q, *J* = 32.9); 132.2; 131.9; 131.5; 130.7; 128.4; 122.2 (q, *J* = 269.1); 116.9; 107.7; 105.5; 102.0; 66.0; 37.5; 24.7; 22.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –59.35. Found, *m*/*z*: 425.1240 $[M+H]^+$. $C_{21}H_{21}ClF_3N_2O_2$. Calculated, *m*/*z*: 425.1244.

Synthesis of pyrazoles 10a–c (General method). Hydrazine hydrate (1.86 ml, 38 mmol) was added to a stirred solution of diketone **9a–c** (1.9 mmol) in EtOH (15 ml). The resulting solution was stirred for 14 h at reflux. Reaction mixture was evaporated to dryness and triturated with cold H_2O.

3-Phenyl-5-(trifluoromethyl)-1*H*-pyrazole (10a) was synthesized from 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**9a**) (1.7 g). Yield 1.52 g (91%), white solid. Spectral data was in accordance with the previously reported.[17]

5-Methoxy-2-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-phenol (10b) was synthesized from 4,4,4-trifluoro-1-(2-hydroxy-4-methoxyphenyl)butane-1,3-dione (**9b**) (500 mg) (synthesized analogously to literature-described procedure[18] from 1-(2-hydroxy-4-methoxyphenyl)ethan-1-one). Yield 397 mg (80%), white solid, mp 149–151°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.59 (1H, d, *J* = 8.5, H-3); 6.97 (1H, s, H-6); 6.61–6.44 (2H, m, H-4 pyrazol, H-5); 3.74 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.6; 155.6; 141.4; 140.9 (q, *J* = 39.0); 128.6; 122.1 (q, *J* = 268.0); 108.1; 105.5; 101.6; 101.4; 55.1. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.28. Found, *m*/*z*: 259.0698 $[M+H]^+$. $C_{11}H_{10}F_3N_2O_2$. Calculated, *m*/*z*: 259.0694.

2-[5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (10c) was synthesized from 4,4,4-trifluoro-1-(2-hydroxyphenyl)-

butane-1,3-dione (**9c**) (390 mg) according to the literature-described procedure.[19] Yield 271 mg (71%), white-beige solid. Spectral data was in accordance with the previously reported.[20]

4-[5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol (10d). Boron tribromide (1 M in CH_2Cl_2, 3.65 ml, 3.65 mmol) was added dropwise to an ice-cooled solution of compound **10b** (236 mg, 0.91 mmol) in CH_2Cl_2 (5 ml). After stirring for 2 h at 25°C, the reaction mixture was poured into ice water, and neutralized with addition of saturated aqueous $NaHCO_3$, followed by extraction with CH_2Cl_2 (2×15 ml). Organic extracts were combined, dried over Na_2SO_4, and evaporated *in vacuo*. Pure product was obtained by trituration with EtOAc – petroleum ether. Yield 31 mg (14%), white solid, mp >220°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 13.32 (1H, br. s, NH); 10.22 (1H, br. s, OH); 9.65 (1H, br. s, OH); 7.45 (1H, d, *J* = 8.5, H-5); 6.90 (1H, s, H-4 pyrazol); 6.44 (1H, d, *J* = 2.2, H-6); 6.31 (1H, dd, *J* = 8.5, *J* = 2.3, H-2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 159.0; 155.6; 141.7; 128.6; 107.2; 106.6; 102.9; 100.9 (CF_3 and C–CF_3 carbons can not be observed due to proton exchange process). ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.24. Found, *m*/*z*: 245.0550 $[M+H]^+$. $C_{10}H_8F_3N_2O_2$. Calculated, *m*/*z*: 245.0538.

4-(4-Chlorophenyl)-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole (12). 4-Bromo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole **11** (405 mg, 1.39 mmol) (synthesized by literature-described procedure[21]) was dissolved in dioxane–H_2O, 4:1 mixture (20 ml) under argon, followed by addition of 4-chlorophenylboronic acid (282 mg, 1.8 mmol), caesium carbonate (1.18 g, 3.62 mmol), and $PdCl_2(PPh_3)_2$ (59 mg, 0.08 mmol). Resulting mixture was heated for 14 h at 100°C. After cooling to room temperature, the reaction mixture was diluted with EtOAc (60 ml), washed with brine (3×60 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was purified by silica gel column chromatography, using gradient from 5 to 20% EtOAc in petroleum ether to obtain product. Yield 118 mg (26%), white solid, mp 187–190°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 11.02 (1H, br. s, NH); 7.45–7.37 (4H, m, H Ar); 7.35–7.21 (5H, m, H Ar). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 142.0; 139.6 (q, *J* = 35.0); 132.9; 132.1; 129.8; 129.2; 129.0; 128.8; 127.9; 125.7; 121.9 (q, *J* = 269.4); 116.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –58.19. Found, *m*/*z*: 323.0571 $[M+H]^+$. $C_{16}H_{11}ClF_3N_2$. Calculated, *m*/*z*: 323.0563.

Synthesis of isoxazoles 13a–e (General method). Hydroxylamine hydrochloride (42 mg, 0.6 mmol) was added to a stirred solution of compound **6c**, **7e**,**f**,**i**,**j** (0.3 mmol) in pyridine (2 ml). The resulting solution was stirred for 14 h at 90°C. After cooling to room temperature, the reaction mixture was poured into H_2O (70 ml) which was acidified with 1 M HCl. Product further was extracted with EtOAc (40 ml), organic layer was washed with brine (3×30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained isoxazoles **13a**,**b**,**d**,**e** were analytically pure and no further purification needed. Isoxazole **13c** was purified by column chromatography on silica gel, using 5 to 30% gradient of EtOAc in petroleum ether.

4-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-benzene-1,3-diol (13a) was synthesized from compound **6c** (130 mg). Yield 115 mg (85%), slightly gray solid, mp 165–168°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.95 (2H, d, *J* = 3.7, 2OH); 7.51–7.45 (2H, m, C_6H_4Cl); 7.30–7.25 (2H, m, C_6H_4Cl); 7.09 (1H, d, *J* = 8.5, H-5); 6.33 (1H, d, *J* = 2.2, H-2); 6.28 (1H, dd, *J* = 8.5, *J* = 2.3, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.3; 161.4; 157.1; 152.6 (d, *J* = 35.2); 133.3; 131.6; 131.1; 128.7; 127.0; 120.0 (q, *J* = 271.8); 113.4; 107.4; 103.6; 102.8. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.58. Found, *m*/*z*: 356.0302 $[M+H]^+$. $C_{16}H_{10}ClF_3NO_3$. Calculated, *m*/*z*: 356.0301.

5-(Benzyloxy)-2-[4-(4-chlorophenyl)-3-(trifluoromethyl)-isoxazol-5-yl]phenol (13b) was synthesized from compound **7d** (130 mg). Yield 129 mg (96%), white solid, mp 141–143°C. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.26 (1H, s, OH); 8.64 (1H, s, H Ar); 7.54–7.27 (9H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 6.62 (1H, dd, *J* = 8.6, *J* = 2.2, H-6); 6.55 (1H, d, *J* = 2.1, H-4); 5.12 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 168.8; 161.9; 157.1; 152.7 (q, *J* = 35.2); 149.4; 136.5; 136.4; 133.4; 131.7; 131.2; 128.7; 128.5; 128.0; 127.8; 126.7; 124.0; 119.9 (q, *J* = 271.8); 114.0; 106.4; 105.4; 102.3; 69.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.58. Found, *m*/*z*: 446.0767 $[M+H]^+$. $C_{23}H_{16}ClF_3NO_3$. Calculated, *m*/*z*: 446.0771.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-(methoxymethoxy)phenol (13c) was synthesized from compound **7f** (190 mg). Yield 124 mg (63%), white solid, mp 119–121°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.6, C_6H_4Cl); 7.25 (2H, d, *J* = 8.5, C_6H_4Cl); 7.00 (1H, d, *J* = 8.8, H-3); 6.65 (1H, d, *J* = 2.4, H-6); 6.53 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.23 (1H, br. s, OH); 5.16 (2H, s, $OC\underline{H}_2OCH_3$); 3.47 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.5; 161.1; 155.8; 154.6 (q, *J* = 36.4); 135.4; 131.3; 130.5; 129.6; 126.0; 119.9 (q, *J* = 272.4); 113.4; 109.7; 106.4; 105.1; 94.3; 56.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.51. Found, *m*/*z*: 400.0550 $[M+H]^+$. $C_{18}H_{14}ClF_3NO_4$. Calculated, *m*/*z*: 400.0563.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-isopropoxyphenol (13d) was synthesized from compound **7i** (124 mg). Yield 125 mg (97%), white solid, mp 111–113°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.6, C_6H_4Cl); 7.25 (2H, d, *J* = 8.4, C_6H_4Cl); 6.95 (1H, d, *J* = 8.8, H-3); 6.46 (1H, d, *J* = 2.4, H-6); 6.36 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.31 (1H, br. s, OH); 4.53 (1H, septet, *J* = 6.0, $OC\underline{H}(CH_3)_2$); 1.33 (6H, d, *J* = 6.1, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 162.0; 156.1; 154.6 (q, *J* = 36.2); 135.4; 131.3; 130.4; 129.6; 126.1; 119.9 (q, *J* = 272.3); 112.3; 109.4; 104.9; 104.0; 70.4; 22.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.54. Found, *m*/*z*: 398.0768 $[M+H]^+$. $C_{19}H_{16}ClF_3NO_3$. Calculated, *m*/*z*: 398.0771.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-(isopentyloxy)phenol (13e) was synthesized from compound **7j** (140 mg). Yield 132 mg (91%), white-yellow solid, mp 112–114°C. ^{1}H NMR spectrum (600 MHz,

$CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.25 (2H, d, *J* = 8.6, C_6H_4Cl); 6.96 (1H, d, *J* = 8.8, H-3); 6.48 (1H, d, *J* = 2.4, H-6); 6.39 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.32 (1H, br. s, OH); 3.97 (2H, t, *J* = 6.7, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.80 (1H, dsept, *J* = 13.4, *J* = 6.7, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.66 (2H, q, *J* = 6.7, $OCH_2C\underline{H}_2CH(CH_3)_2$); 0.95 (6H, d, *J* = 6.7, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (151 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 163.1; 156.0; 154.6 (q, *J* = 36.1); 135.4; 131.3; 130.3; 129.6; 126.1; 119.9 (q, *J* = 272.4); 112.9; 108.7; 105.0; 103.1; 66.9; 37.8; 25.2; 22.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.54. Found, *m*/*z*: 426.1085 $[M+H]^+$. $C_{21}H_{20}ClF_3NO_3$. Calculated, *m*/*z*: 426.1084.

4-(4-Chlorophenyl)-5-[2-methoxy-4-(methoxymethoxy)-phenyl]-3-(trifluoromethyl)isoxazole (14). Methyl iodide (53 μl, 0.85 mmol) was added to a stirred solution of compound **13c** (114 mg, 0.285 mmol) with K_2CO_3 (98 mg, 0.71 mmol) in DMF (2 ml) at room temperature. The reaction mixture was stirred for 14 h and then partitioned between EtOAc (20 ml) and brine (10 ml). Organic layer was separated, washed with brine (2×20 ml), dried over anhydrous Na_2SO_4 to obtain pure product. Yield 117 mg (99%), colorless oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.36 (1H, d, *J* = 8.6, H-6); 7.32 (2H, d, *J* = 8.6, C_6H_4Cl); 7.17 (2H, d, *J* = 8.4, C_6H_4Cl); 6.69 (1H, dd, *J* = 8.6, *J* = 2.2, H-5); 6.53 (1H, d, *J* = 2.2, H-3); 5.20 (2H, s, $OC\underline{H}_2OCH_3$); 3.49 (3H, s, $OCH_2OC\underline{H}_3$); 3.40 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.7; 161.3; 158.1; 153.8 (q, *J* = 36.1); 134.4; 131.8; 130.6; 128.8; 127.6; 120.2 (q, *J* = 272.2); 114.6; 109.1; 108.1; 100.5; 94.5; 56.5; 55.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.32 Found, *m*/*z*: 414.0734 $[M+H]^+$. $C_{19}H_{16}ClF_3NO_4$. Calculated, *m*/*z*: 414.0720.

4-[4-(4-Chlorophenyl)-3-(trifluoromethyl)-isoxazol-5-yl]-3-methoxyphenol (15). 12 M HCl (30 μl, 0.97 mmol) was added to a stirred solution of isoxazole **14** (88 mg, 0.21 mmol) in MeOH (3 ml), and the reaction mixture was heated at 60°C for 3 h. After cooling to room temperature, reaction mixture was evaporated to dryness, partitioned between EtOAc (10 ml) and brine (10 ml). Organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to obtain pure product. Yield 76 mg (97%), white-yellow solid, mp 148–150°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.35–7.28 (3H, m, H Ar); 7.16 (2H, d, *J* = 8.4, C_6H_4Cl); 6.47 (1H, dd, *J* = 8.4, *J* = 2.3, H-6); 6.37 (1H, d, *J* = 2.3, H-2); 5.38 (1H, br. s, OH); 3.39 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 159.8; 158.4; 153.8 (q, *J* = 36.1); 134.4; 132.1; 130.6; 128.8; 127.6; 120.1 (q, *J* = 272.1); 114.5; 108.2; 108.0; 99.7; 55.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.32. Found, *m*/*z*: 370.0457 $[M+H]^+$. $C_{17}H_{12}ClF_3NO_3$. Calculated, *m*/*z*: 370.0458.

3-(4-Chlorophenyl)-4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl trifluoromethanesulfonate (16). Trifluoromethanesulfonic anhydride (530 μl, 3.22 mmol) was added dropwise under ice cooling to a stirred solution of compound **6c** (1 g, 2.93 mmol) and Et_3N (818 μl, 5.87 mmol) in dry CH_2Cl_2 (40 ml). After 1 h of stirring at room temperature, reaction mixture was poured into H_2O, oganic layer was washed with brine (20 ml), separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography using 5% EtOAc in petroleum ether. Yield 1.32 g (95%), light-yellow oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.35 (1H, d, *J* = 8.9, H-5); 7.58 (1H, d, *J* = 2.3, H-8); 7.51–7.35 (3H, m, H Ar); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.6; 155.4; 153.2; 149.4 (q, *J* = 36.5); 135.7; 131.2; 129.4; 128.9; 126.7; 125.4; 122.9; 120.5; 120.4; 120.1; 117.7; 117.2; 112.0. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.60; –72.50. Found, *m*/*z*: 472.9687 $[M+H]^+$. $C_{17}H_8ClF_6O_5S$. Calculated, *m*/*z*: 472.9685.

3-(4-Chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (17). Triethylsilane (1.12 ml, 7 mmol) and $PdCl_2(PPh_3)_2$ (98 mg, 0.14 mmol) were added to a stirred solution of compound **16** (1.32 g, 2.8 mmol) in DMF (15 ml) at room temperature. The reaction mixture was allowed to heat at 60°C for 1 h. After cooling to room temperature, reaction mixture was partitioned between EtOAc (30 ml) and brine (20 ml). Organic layer was separated, washed with brine (2×20 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude residue was crystallized from petroleum ether to obtain pure product. Yield 530 mg (58%), yellow solid, mp 107–109°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.24 (1H, dd, *J* = 8.0, *J* = 1.6, H-5); 7.80 (1H, ddd, *J* = 8.6, *J* = 7.2, *J* = 1.7, H-7); 7.59 (1H, d, *J* = 8.5, H-8); 7.50 (1H, t, *J* = 7.6, H-6); 7.44 (2H, d, *J* = 8.4, C_6H_4Cl); 7.21 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 176.8; 155.2; 148.8 (q, *J* = 36.3); 135.3; 135.2; 131.4; 128.7; 127.6; 126.6; 126.5; 124.6; 123.3; 119.4 (q, *J* = 277.0); 118.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.60. Found, *m*/*z*: 325.0249 $[M+H]^+$. $C_{16}H_9ClF_3O_2$. Calculated, *m*/*z*: 325.0243.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-phenol (18). Hydroxylamine hydrochloride (227 mg, 3.26 mmol) was added to a stirred solution of compound **17** (530 mg, 1.63 mmol) in pyridine (5 ml). The resulting solution was stirred for 14 h at 90°C. After cooling to room temperature, the reaction mixture was poured into H_2O (100 ml) which was acidified with 1 M HCl. Product further was extracted with EtOAc (60 ml), organic layer was washed with brine (3×30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Yield 550 mg (99%), pink solid, mp 147–150°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40–7.33 (3H, m, C_6H_4Cl, H Ar); 7.27–7.22 (2H, m, C_6H_4Cl); 7.14 (1H, dd, *J* = 7.9, *J* = 1.7, H-3); 6.96 (1H, dd, *J* = 8.3, *J* = 1.1, H-4); 6.88 (1H, ddd, *J* = 7.8, *J* = 7.3, *J* = 1.1, H-6); 6.04 (1H, br. s, OH). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.4; 154.5 (q, *J* = 36.4); 154.2; 135.5; 133.1; 131.1; 129.8; 129.5; 125.9; 121.1; 119.9 (q, *J* = 272.4); 117.9; 114.7; 112.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.42. Found, *m*/*z*: 340.0341 $[M+H]^+$. $C_{16}H_{10}ClF_3NO_2$. Calculated, *m*/*z*: 340.0352.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-phenyl trifluoromethanesulfonate (19). Trifluoromethanesulfonic anhydride (200 μl, 1.22 mmol) was added dropwise under ice cooling to a stirred solution of compound **18** (295 mg, 0.87 mmol) and triethylamine (242 μl, 1.74 mmol) in

dry CH_2Cl_2 (10 ml). After 1 h of stirring at room temperature, the reaction mixture was poured into H_2O, oganic layer was washed with brine (15 ml), separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography, using 5% EtOAc in petroleum ether. Yield 399 mg (97%), light-yellow oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.60 (1H, ddd, *J* = 8.3, *J* = 6.8, *J* = 2.5, H-6); 7.44–7.33 (5H, m, C_6H_4Cl, H Ar); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 164.3; 154.2 (q, *J* = 36.7); 146.6; 135.7; 133.2; 131.8; 130.9; 129.5; 129.0; 125.0; 123.2; 120.5; 118.6 (q, *J* = 320.9); 119.8 (q, *J* = 272.4); 117.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.36, –73.40. Found, *m*/*z*: 471.9847 $[M+H]^+$. $C_{17}H_9ClF_6NO_4S$. Calculated, *m*/*z*: 471.9845.

4-(4-Chlorophenyl)-5-phenyl-3-(trifluoromethyl)-isoxazole (20). Triethylsilane (772 μl, 4.83 mmol) and $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) were added to a stirred solution of compound **19** (380 mg, 0.8 mmol) in DMF (7 ml) at room temperature. Reaction mixture was allowed to heat at 60°C for 1 h. After cooling to room temperature, the reaction mixture was partitioned between EtOAc (20 ml) and brine (20 ml). Organic layer was separated, washed with brine (2×10 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography, using gradient from 1 to 5% EtOAc in petroleum ether. Yield 190 mg (73%), white solid, mp 88–90°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.54–7.47 (2H, m, H-2,6); 7.47–7.41 (3H, m, H Ar); 7.41–7.34 (2H, m, H Ar); 7.29 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 168.2; 154.8 (q, *J* = 36.1); 135.5; 131.6; 131.1; 129.6; 129.2; 127.2; 126.3; 126.1; 119.9 (q, *J* = 272.2); 113.2. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.64. Found, *m*/*z*: 324.0398 $[M+H]^+$. $C_{16}H_{10}ClF_3NO$. Calculated, *m*/*z*: 324.0403.

5-Phenyl-3-(trifluoromethyl)isoxazole (21a). Hydroxylamine hydrochloride (1.74 g, 25 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**9a**) (1.8 g, 8.33 mmol) in EtOH (50 ml) at room temperature. The reaction mixture was allowed to heat at 80°C for 3 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (50 ml) and 1 M HCl (20 ml). Organic layer was separated, washed with brine (2×20 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained residue then was dissolved in glacial AcOH (25 ml), and 98% H_2SO_4 (2 ml, 37.5 mmol) was added dropwise. The resulting mixture was heated at 100°C for 1 h and cooled down to room temperature followed by evaporation *in vacuo*. After trituration of crude residue with cold H_2O, solid precipitated from the solution. This solid was filtered off, the filter cake was washed several times with distilled H_2O and dried in air. Yield 1.125 g (63%), beige crystals. Spectral data was in accordance with those previously reported.[22]

5-Methoxy-2-[3-(trifluoromethyl)isoxazol-5-yl]phenol (21b). Hydroxylamine hydrochloride (341 mg, 4.91 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-(2-hydroxy-4-methoxyphenyl)butane-1,3-dione (**9b**) (600 mg, 2.3 mmol) in pyridine (7 ml) at room temperature. The reaction mixture was allowed to heat at 100°C for 3 h. After cooling to room temperature, reaction mixture was partitioned between EtOAc (30 ml) and 1 M HCl (30 ml). Organic layer was separated, washed with brine (2×30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained residue then was dissolved in glacial AcOH (10 ml), and 98% H_2SO_4 (500 μl, 9.38 mmol) was added dropwise. The resulting mixture was heated at 100°C for 1 h and cooled down to room temperature followed by evaporation *in vacuo*. After trituration of crude residue with cold H_2O, solid precipitated from the solution. This solid was filtered off, filter cake was washed several times with distilled H_2O and dried in air. Crude compound was purified by trituration with hot EtOAc – petroleum ether 1:3 mixture to obtain pure product. Yield 242 mg (38%), beige crystals, mp >150°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.98 (1H, s, OH); 7.76 (1H, d, *J* = 9.5, H-3); 7.12 (1H, s, H-4 isoxazole); 6.63–6.58 (2H, m, H-4,6); 3.78 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.5; 162.8; 156.9; 155.0 (q, *J* = 37.0); 128.2; 120.0 (q, *J* = 270.9); 106.4; 105.8; 101.4; 98.0; 55.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.25. Found, *m*/*z*: 260.0530 $[M+H]^+$. $C_{11}H_9F_3NO_3$. Calculated, *m*/*z*: 260.0535.

MIC assay. All of the compounds for the MIC tests had the purity level not lower than 95%. *Staphylococcus aureus* strain Newman was cultured overnight at 37°C in Mueller Hinton broth (MHB) (Oxoid). The MIC was determined using the microdilution method according to guidelines of the Clinical Laboratory Standards Institute.[7] In a 96-well plate, a series of twofold dilutions of each compound were added to a 1:100 dilution of an overnight culture of *S. aureus* in a final volume of 100 μl and incubated overnight at 37°C. The final concentration of the compounds was in a range 50–0.39 μg/ml. MIC was determined as the lowest concentration where no growth was detected by measurement of optical density at 600 nm (OD600). Compounds that did not inhibit growth were retested at higher concentrations (250–1.95 μg/ml). Wells containing bacteria with or without 1% DMSO and medium alone were included as controls in every plate.

Supplementary information file containing ^{1}H, ^{13}C, ^{19}F NMR spectra and HRMS data of all synthesized compounds is available at the journal website http://link.springer.com/journal/10593.

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