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Reactions of CF₃-enones with arenes under superelectrophilic activation: a stereoselective pathway to *trans*-1,3-diaryl-1-trifluoromethyl indane scaffold as a new core for cannabinoid receptor ligand design

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Keywords

CF₃-enones, Brønsted superacids, trifluoromethyl group, indanes, endocannabinoid system, cannabinoid receptor ligands

Abstract

4-Aryl-1,1,1-trifluorobut-3-en-2-ones ArCH=CHCOCF$_3$ (CF$_3$-enones) react with arenes in excess of Brønsted superacids (TfOH, FSO$_3$H) to give, stereoselectively, *trans*-1,3-diaryl-1-trifluoromethyl indanes in 35-85% yields. The reaction intermediates, the O-protonated ArCH=CHC(OH$^+$)CF$_3$ and the O,C-diprotonated ArHC$^+$CH$_2$C(OH$^+$)CF$_3$ species, have been studied by means of ^{1}H, ^{13}C, ^{19}F NMR, and DFT calculations. Both types of the cations may participate in the reaction, depending on their electrophilicity and electron-donating properties of the arenes. The formation of CF$_3$-indanes is a result of cascade reaction of protonated CF$_3$-enones to form chemo-, regio- and stereoselectively three new C-C bonds. The obtained *trans*-1,3-diaryl-1-trifluoromethyl indanes were investigated as potential ligands for cannabinoid receptors CB$_1$ and CB$_2$ types. The most potent compound showed sub-micromolar affinity for both receptor subtypes with a 6-fold selectivity toward CB$_2$ receptor with no appreciable cytotoxicity toward SHSY5Y cells.

Graphical Abstract
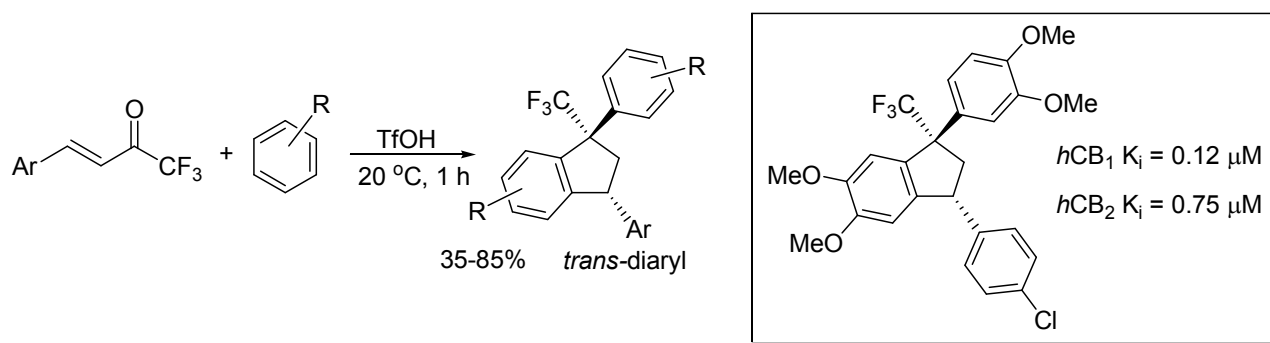
Introduction

1,1,1-Trifluorobut-3-en-2-ones (CF$_3$-enones) are important fluorinated building blocks having rich chemistry and are used frequently for preparation of practically valuable fluorine-containing substances. Several approaches to synthesis of CF$_3$-enones have been developed.[1] The combination of a conjugated carbon-carbon double bond and a CF$_3$CO-group present in these compounds, results in

their unique electrophilic properties, leading to the reactions at either the carbonyl group[2] or the double bond[3] - or at both of these structural fragments.[4] CF$_3$-enones are known to react with various *O*-, *S*-, *N*-, *C*-nucleophiles to give numerous polyfunctional derivatives, carbo- and heterocycles bearing a trifluoromethyl group. Many of those have been shown to possess diverse biological activities.[5]

In continuation of our previous studies of reactions of CF$_3$-alkynes in Brønsted superacids,[6] and CF$_3$-allyl alcohols under action of Lewis acids,[7] we became interested in studying of the fate of CF$_3$-enones **1a-h** (Figure 1) under similar superelectrophilic activation. In preliminary short communication[8] we showed that 1,1,1-trifluoro-4-phenylbut-3-en-2-one **1a** reacted with benzene, o-xylene, and veratrole in TfOH. We chose Brønsted superacids (TfOH, FSO$_3$H)[9] to significant enhancement of electrophilic properties of CF$_3$-enones system by protonation. The main goal of this work was to investigate the protonation of butenones **1a-h** in superacids, the subsequent reactions of the resulting carbocations with arenes, as π-nucleophiles, and to test physiological activity of the resulting trifluoromethylated compounds.
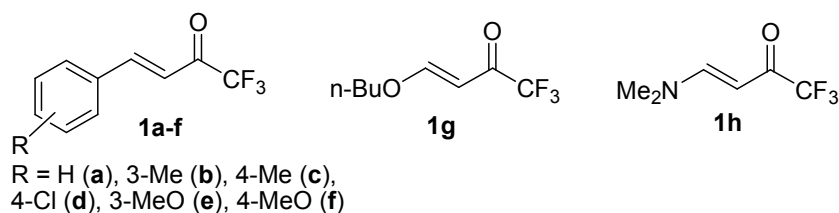

R = H (**a**), 3-Me (**b**), 4-Me (**c**),
4-Cl (**d**), 3-MeO (**e**), 4-MeO (**f**)

Figure 1. Starting CF$_3$-enones **1a-h** used in this study

Results and discussion

DFT calculation of cations derived from of 4-aryl-1,1,1-trifluorobut-3-en-2-ones

Protonation of conjugated enones[9a,b] or ynones[9c] in Brønsted superacids proceeds in two steps: first, protonation of the carbonyl oxygen occurs, followed by second protonation of unsaturated carbon-carbon bond. In the same way protonation of CF$_3$-enones system of compounds **1** gives consequently cations **A** and dications **B** (Scheme 1). The latter species are considered as superelectrophiles.[9b] Both the O-protonated (**A**) and the O,C-diprotonated (**B**) forms can be reactive

electrophiles. They have two carbocationic centers (at C^2 and C^4) that may participate in further reactions.
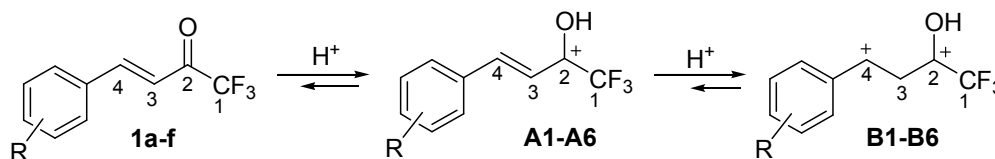
Scheme 1 Protonation of CF_3-enones

To have insight into the nature of formed electrophilic species we decided to study the reaction of CF_3-enones with acids theoretically. In order to estimate the charge distribution in these species (as well as their electrophilicity), we performed DFT calculations for carbocations, derived from CF_3-enones **1a-f** (Scheme 1). Selected electronic characteristics of the O-protonated forms (**A1-A6**), the O,C-diprotonated forms (**B1-B6**) are presented in SI (Table S9). The global electrophilicity index can be used quite effectively to sort various electrophiles qualitatively and provide a good estimation of the activity of electrophiles. This parameter is easily calculated from the HOMO and LUMO levels.[10]

The data obtained shows that the highest value of global electrophilicity index ω 30.3-47.5 eV belongs to dication **B1-B6**. That is quite predictable for doubly charged species.[9,11] Apart from that, these dications have a large positive charge (0.66-0.69 e) and a great contribution of an atomic orbital in LUMO on C^2 atom (18.2-34.6%) which indicates a combined effect of charge and orbital control on reactivity of that carbon atom. This also reveals that the O,C-diprotonated species **B** should be extremely reactive electrophiles (superelectrophiles[9b]) with the C^2 atom being more reactive compared C^4.

The O-monoprotonated cations **A1-A6** also carries a bigger positive charge on C^2 (0.40-0.43e) atom compared C^4 (0.02-0.07 e). However, the latter has a slightly bigger contribution of atomic orbital to LUMO (26.5-29.7 %). It may determine the predominance of orbital control in reactivity of C^4 atom for cations **A1-A6**.

4

Thus, the DFT calculations predict that in principle both cationic species **A** and **B** derived from **1** (Scheme 1) may act as electrophiles. Atom C^2 is the reactive center in dications **B**. Cations **A** may possess two centers (atoms C^2 and C^4) for the reaction with nucleophiles.

NMR study of CF_3-enones protonation in superacids

In order to confirm DFT predictions we investigated protonation of CF_3-enones in TfOH and FSO_3H at various temperatures by means of NMR. It was found, that CF_3-enones **1a,c,d,f,h** afforded stable O-protonated species **A1**, **A3**, **A4**, **A6**, **A7**, respectively, at temperatures below -20 °C. ^{1}H, ^{13}C, and ^{19}F NMR data of these carbocations and the corresponding starting materials are given in SI (Table S1). ^{13}C NMR signals of ions **A1**, **A3**, **A4**, **A6**, **A7** were carefully assigned using HSQC (C–H) experiments. The signal of proton bounded to the carbonyl oxygen was not detected, due to a fast proton exchange with superacidic media.[9] At higher temperatures (above -20 °C), subsequent protonation of the carbon-carbon double bond can take place and the corresponding superelectrophilic dications **B** are formed. Unfortunately, we failed to detect these dications in the NMR spectra, due to their extreme instability and high reactivity, which is peculiar to superelectrophiles.[9b] At higher temperatures (-20…0 °C), the spectral data pointed out the formation of complex mixtures of oligomeric reaction products (vide infra). Contrary to other CF_3-enones, compound **1h** gave extremely stable (even at 60 °C) and unreactive cation **A7** .
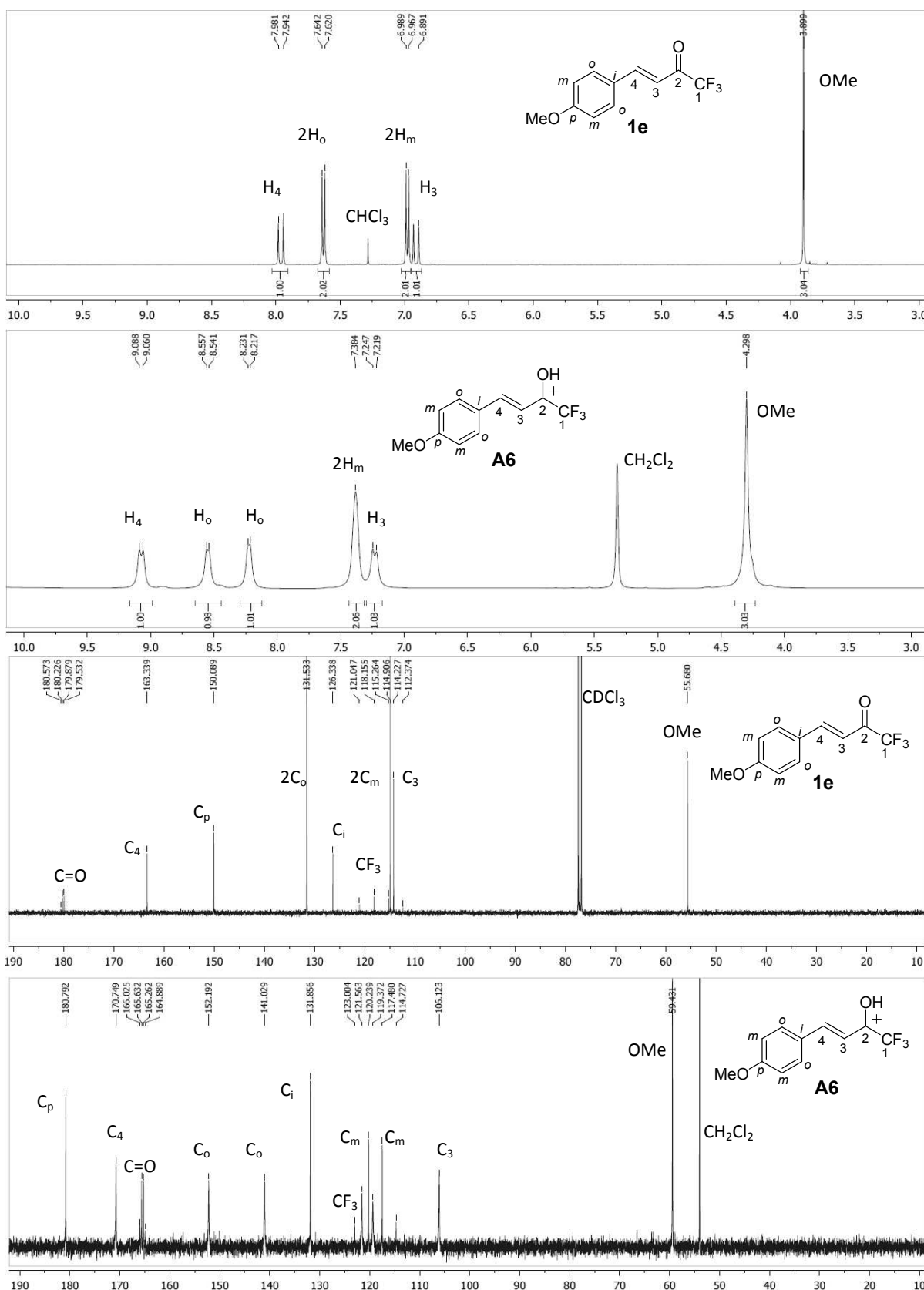
Figure 2 Comparison of ^{1}H and ^{13}C NMR spectra of **1f** (CDCl$_3$, 20 °C) and cation **A6** (FSO$_3$H, -60 °C).

Comparison of the spectra of aryl substituted cations **A1**, **A3**, **A4**, **A6** and their neutral precursors **1a,c,d,f** revealed that the signals corresponding to proton H^4 and carbon C^4 underwent substantial downfield shifts: $\Delta\delta_H \sim 1.1\text{-}1.7$ ppm in ^{1}H NMR and $\Delta\delta_C \sim 20\text{-}30$ ppm in ^{13}C NMR (Table S1, Figure 2). Such spectral changes indicated a partial positive charge delocalization on carbon C^4 and contribution of the corresponding resonance structure **A'** (Table S1). On the other hand, the carbonyl carbon C^2 (in ^{13}C NMR) underwent only slight upfield shifts upon protonation. That additionally argues in favor of form **A'**. Apart from that, in ^{1}H and ^{13}C NMR spectra of species **A1**, **A3**, **A4**, **A6** the signals of the ortho- and meta- protons and carbons of the aromatic ring are non-equivalent. That indicates a contribution of another resonance structure **A''** (Table S1), in which restricted rotation around bond C^4–C_i is possible. This resonance form has a significant contribution in case of para-methoxy substituted cation **A''6**, in which the signal of C_p atom is shifted to 180.8 ppm, compared to 150.1 ppm in the non-protonated starting material **1f** (see Figure 2). Dimethylamino substituted cation is also characterized by resonance **A'7** (Table S1).

Thus, NMR data indicates a significant delocalization of positive charge from C^2 to C^4 in the O-protonated species **A**, despite the fact that the DFT calculations did not predict a substantial charge re-distribution (see Table S9). These data suggest that carbocations **A** are likely to react with nucleophiles primarily at C^4.

Reaction of CF$_3$-enones with arenes in superacids

Having gathered the NMR data relevant to the protonation of CF$_3$-enones **1**, we proceeded to study the behavior of compounds **1** in superacids. In TfOH at 20 °C, CF$_3$-enones **1a-c,e** are converted quantitatively into mixtures of oligomers consisting of at least 6 units of the starting butanone (according to MALDI mass spectrometry data, see SI). Indeed, the observed oligomerization is a likely fate for dications **B** formed in the absence of intercepting nucleophiles in the reaction medium.

Table 1. Reactions of CF$_3$-enone **1a** with benzene (12 equiv.) under the action of various acids
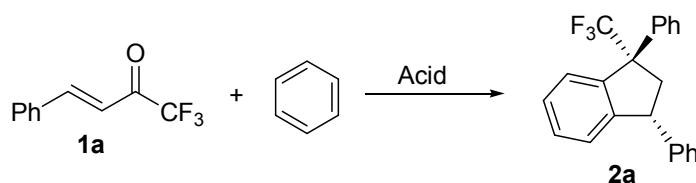
Entry	Reaction conditions			Reaction products
	Acid	T, °C	t, h	(yield, %)
1	**TfOH (50 equiv.)**	**20**	**1**	**2a (84%)**[a]
2	TfOH (5 equiv.), CH$_2$Cl$_2$(co-solvent)	20	1	**2a** (8%)[a]
3	TfOH (1 equiv.), CH$_2$Cl$_2$(co-solvent)	20	1	traces of **2a**[b]
4	H$_2$SO$_4$ (750 equiv.)	20	18	**2a** (15%)[a]
5	FSO$_3$H (80 equiv.), SO$_2$(co-solvent)	-40	3	**1a** (100%)[c]
6	FSO$_3$H (80 equiv.)	20	1	oligomers
7	TfOH (50 equiv.)	-20	3	**1a** (100%)[c]
8	AlBr$_3$ (5 equiv.)	20	0.5	oligomers[a]
9	AlBr$_3$ (5 equiv.), CH$_2$Cl$_2$(co-solvent)	-40	1	**1a** (100%)[c]
10	AlCl$_3$ (5 equiv.), CH$_2$Cl$_2$(co-solvent)	20	1	oligomers[a]
11	FeCl$_3$ (5 equiv.)	20	1	**1a** (100%)[c]

Notes. [a]Complete conversion of initial **1a**. [b]Incomplete conversion (~30%) of initial **1a**. [c]Quantitative recovery of unreacted initial **1a**.

We were then curious to see if addition of carbocation aromatic traps, such as benzene or other arenes, would change the course of the transformation of butenones **1** in superacids (Table 1, Schemes 2, 3). Under the conditions that give rise to species **A1** (-40…-20 °C, FSO_3H or TfOH), CF_3-enones **1a** demonstrated no appreciable conversion in the presence of an excess amount of benzene (Entries 5, 7, Table 1). Also, in TfOH cations **A3** (at -20 °C) and **A7** (even on heating up to 60 °C), derived from compounds **1c** and **1h**, correspondingly, did not react with benzene. Thus, these particular O-protonated forms (**A1, A3, A7)** are not reactive toward benzene under these conditions.

The reaction of compound **1a** with benzene in neat TfOH at 20 °C (i.e. when intermediate dication **B1** is likely to be formed) afforded indane **2a** in 84 % yield (Entry 1, Table 1). Use of less amount of TfOH gave unsatisfactory results (Entries 2,3). Compared to TfOH, other Brønsted (Entries 4, 6) or Lewis (Entries 8-11) acids were not as efficient in promoting of the same transformation.

The obtained indane **2a** is the result of a very deep transformation of **1a**, in which both carbons C^2 and C^4 participate in the reaction. It should be pointed out that two molecules of benzene participated in the reaction and three new carbon-carbon bonds are formed. Quite significant is also stereochemistry of the reaction. According to the NMR data, only one diastereomer is formed having *trans*-arranged phenyl groups in cyclopentane ring of indane system.

For comparison, other conjugated enones, such as alkene carbaldehydes or ketones,[12a-c] alkene carboxylic acids[12d-j] and their chloro anhydrides[12k-l] or amides,[m-q] undergo hydroarylation of carbon-carbon double bond in reactions with arenes under activation with Bronsted superacids, strong Lewis acids or acidic zeolites. But in the reactions of these enones carbonyl group remains unaffected. Introduction of electron-withdrawing CF_3-substituent to enone system of **1a** leads to additional electrophilic activation of carbonyl carbon C^2, which takes part in reaction with benzene (Table 1). It should be also noted that for some enones[12f,q-t] the formation of stable O,C-diprotonated species (like dications **B**, Scheme 1) in superacids was detected by means of NMR.

The structures of indanes **2** (vide infra) were unambiguously determined by means of ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, high-resolution mass-spectrometry, and X-ray (Figure 4). The relative

stereochemistry of products **2** was established by NOESY experiments (Figure 3). It should be noted that this reaction is highly stereoselective, leading to indane with exclusively *trans*-orientation of aryl groups. In addition we studied the molecular structure of **2a** by X-ray crystallography. The structure was totally in agreement with NMR data to confirm *trans*-orientation of phenyl rings (see Figure 4a).
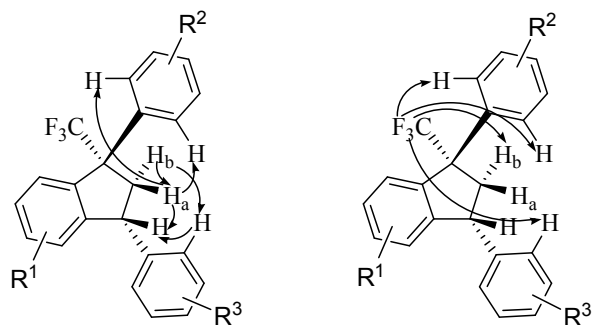

Figure 3. ^{1}H, ^{1}H NOESY (left) and ^{1}H, ^{19}F HOESY (right) correlations, proving stereochemical configuration of indanes **2**
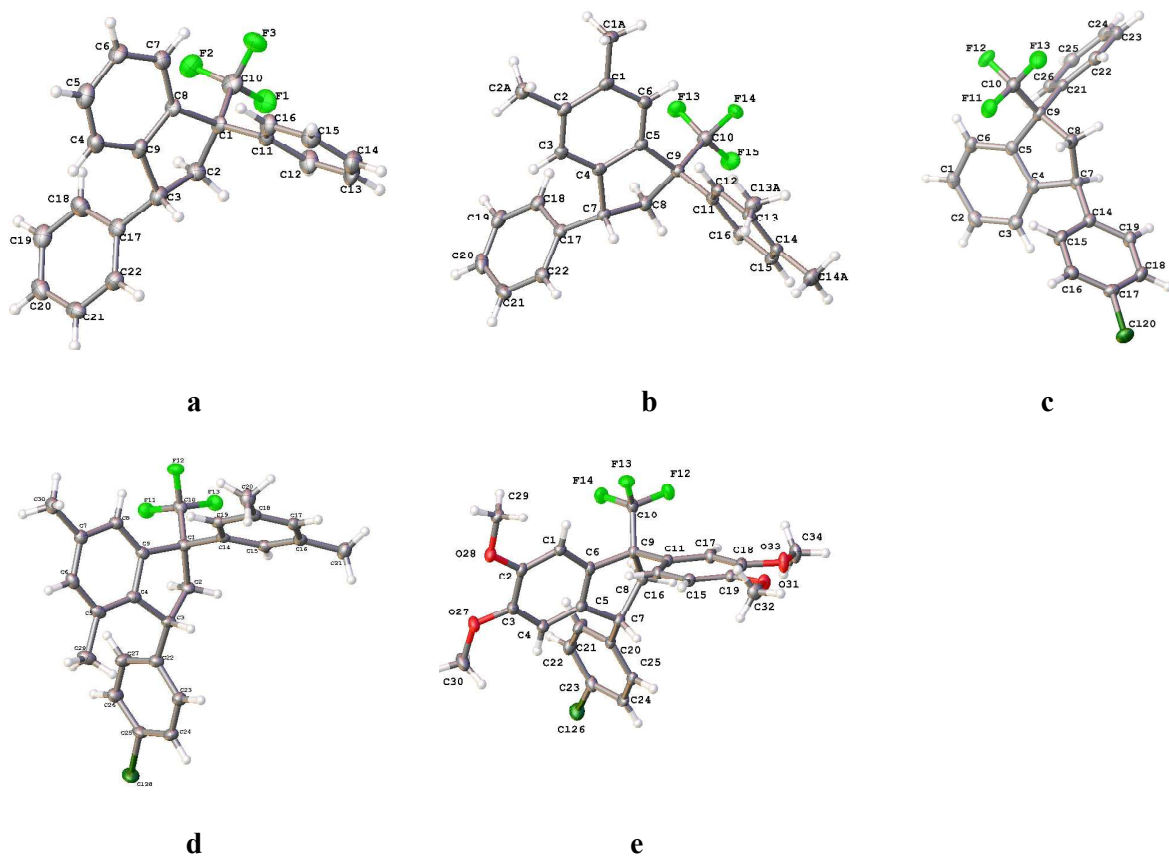

a   b   c

d   e

Figure 4. X-ray crystal structures of compounds **2a** (a), **2b** (b), **2e** (c), **2g** (d), **2h** (e) (ellipsoid contour of probability levels are 50%)

Indane (indene) fragment is a very important structural unit of a large number of bioactive and pharmaceutically interesting molecules as well as modern catalysts for polymerization. 2-Trifluormethylated indanes are an important type of indane derivatives, which have been used in biological study as well as precursors for indene synthesis. However, so far the existing approaches to trifluoromethylated indanes have some restrictions.[12i, 13] The synthesis proposed in this investigation is quite straightforward to construct highly desirable CF_3-indane derivatives from arene and the corresponding CF_3-enones in one-pot sequence.

Having found the reaction conditions leading to the formation of indane **2a** (TfOH, 20 °C, 1 h) we decided to study scope of the reaction and possible mechanism of the transformation. For this aim a set of arenes and CF_3-enones **1a-h** were studied under conditions of superelectrophilic activation (see Experimental). It was found, that enone **1a** reacts in a similar way with other arenes, for example, *o*-xylene and 1,2-dimethoxybenzene (veratrol) to form trifluoromethylated indanes **2b, 2c** in high yields (Scheme 2). Similar adducts **2e-h** were isolated in good to high yields by the reaction of enone **1d** with benzene, *o*- and *m*-xylenes and veratrol (electron rich aromatics). Compound **2d** was obtained from reaction of **1c** with benzene. It should be pointed out that in all cases we observed the highly stereoselective formation of trifluoromethylated indanes. Accordingly to the reaction mechanism (vide infra) the cyclization in the case of the reaction of enones with aromatics having different substituents could result in formation of mixture of cyclization products, however as a rule the reaction proceeds highly chemoselectively and the cyclization proceeds into the most nucleophilic aromatic ring. The structures of some indanes were confirmed using X-ray data (Figure 4).
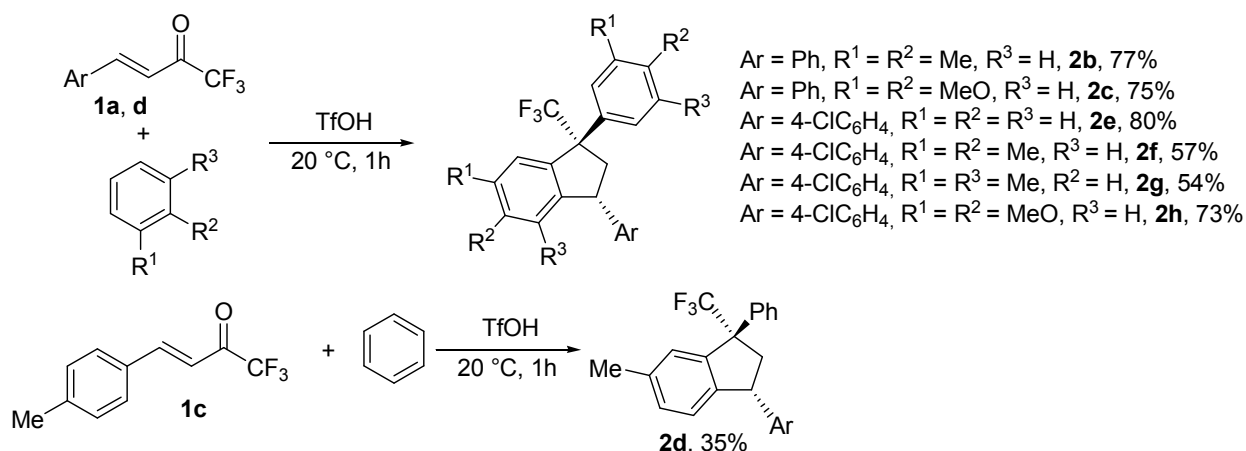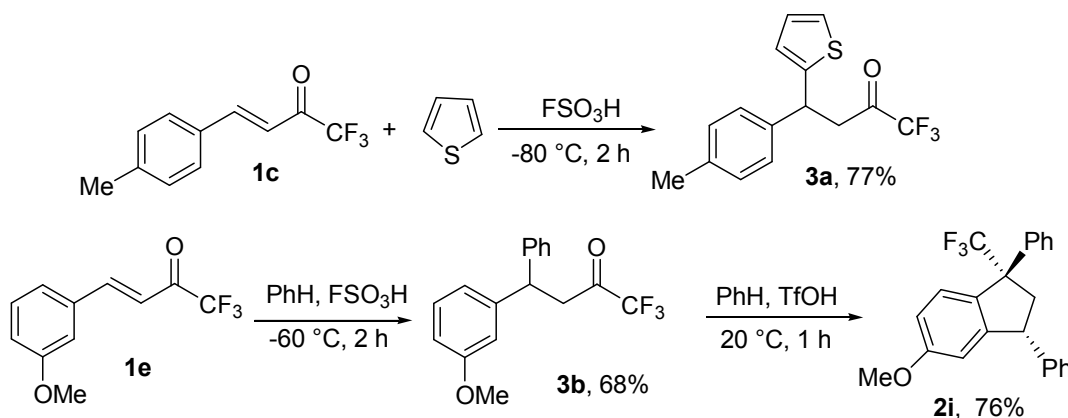
Scheme 2. Reaction of CF$_3$-enones **1a,c,d** with electron rich aromatics

We found that the reaction is extremely sensitive to steric demands. To our surprise the reaction of enone **1d** with *m*-xylene resulted not in the expected product of the attack to 4-position of *m*-xylene but the formation of 2-trifluoromethylated indane **2g**, bearing 3,5-dimethylphenyl group at C-2 atom. Accordingly X-ray data (Figure 4d) exactly this aromatic ring is attached to the indane core. We believe that this regiochemistry can be explained by high steric bulkness of CF$_3$ group which has quite significant conformation energy 2.1 kcal/mol.[14] As a result in the case of the reaction with *m*-xylene thermodynamically controlled electrophilic substitution is observed.

For molecules of all studied compounds **2a,b,e,g,h** (Figure 4) pentagonal ring of the indane system is a regular envelope with atoms C^1, C^3, C^4, C^5 as base and C^1, C^2, C^3 as lid. Angle between base and lid planes of envelope change from 35.66(9)° for **2g** to 32.0(1)° for **2c**. CF$_3$-group deviates to the envelope lid (the angle of deviation change weakly from 110.6 (1)° for **2h** to 111.9(1)° for **2g**). The benzene ring plane of the indane system has no deviation from envelope base plate practically (limits are from 0.3(1)° for **2b** to 3.1(1)° for 2g). Planes of aryl substituents are bended to envelope base with angle 72.33(6)° for **2g** ÷ 77.1(1)° for **2a** and 66.74(9)° for **2h** ÷ 76.90(6)° for **2b** of the indane system atoms C^1 and C^3, correspondingly. The analysis of molecule conformations of these five studied compounds (Figure 4), having no substituents at atom C^2 of indane system, and published

earlier compounds **11g**, **13** shows that variation of substituents at atoms C^1 and C^3 of indane system changes very slightly the configuration of indane core.[13f,15]

The formation of indanes **2** indicates that both electrophilic carbons C^2 and C^4 of cationic intermediates **A** or **B** participated in the reaction. Interestingly, electron-rich substrates, such as *o*-xylene or thiophene, reacted with CF_3-enones **1a,c** in FSO_3H at -80…-60 °C, i.e. under the conditions that favor the formation of O-protonated species **A1**, **A3** (see Table S1). We also obtained very interesting results under these conditions to give clues to the reaction mechanism. We were able to stop reaction at the first step and isolate in very good yields the products of hydroarylation of enones **2**, which are most probably the intermediates of this reaction formed on the first step of the reaction sequence. For example, the reaction of enone **1c** with thiophene (-80 °C, FSO_3H) gave only the corresponding 3,3-diarylbutanone **3a** in 77 % yield (Scheme 3). The reaction of CF_3-enone **1e** with benzene in FSO_3H at -60 °C gave CF_3-enone **3b** in 68 % yield (Scheme 3). In addition we confirmed that these type of compounds can be transformed into indanes. For instance, the reaction of **3b** with benzene in TfOH at 20 °C gave the expected indane **2i** in 76 % yield (Scheme 3).


Scheme 3. Stepwise addition of arenes to CF_3-enones **1**

All these data clearly demonstrate that cations **A** are generally able to react at C^4 with electron rich arenes and heteroarenes. However, the highly electrophilic versions of these cations, like **A5** (based on its ω values presented in Table S9) generated from **1e**, can also react with less nucleophilic

arenes like benzene, also at C^4 (Scheme 3). Finally, we believe that the reactions of CF_3-enones **1a-d,f** with benzene in TfOH at 20 °C are likely to proceed via the intermediate formation of dications **B**.

Discussion on reaction mechanism

Analyzing DFT calculations obtained for cations **A, B** (Tables S9), NMR (Table S1) and experimental data (Table 1, Schemes 2,3), we conclude that species **A** and **B** initially can react with nucleophiles at C^4 and C^2 respectively. Based on this conclusion, one can propose the following reaction pathways for the transformation of CF_3-enones **1** into indanes **2** (Scheme 4). The reaction of arenes with cation **A** at carbon C^4 can give compound **3**, subsequent protonation leads to formation of cation **D**. The latter one can react further in two ways: intermolecularly, with the arene, to give rise to compound **4**, or intramolecularly - to afford after cyclization indanol **5**. Compounds **4** and **5** may also be obtained via the reaction of dication **B** with an arene at C^2 to result in the formation of cation **E**. Subsequent transformations of **4** and **5** can proceed with an intermediate formation of cations **F** and **G**, respectively, culminating the formation of indanes **2**.
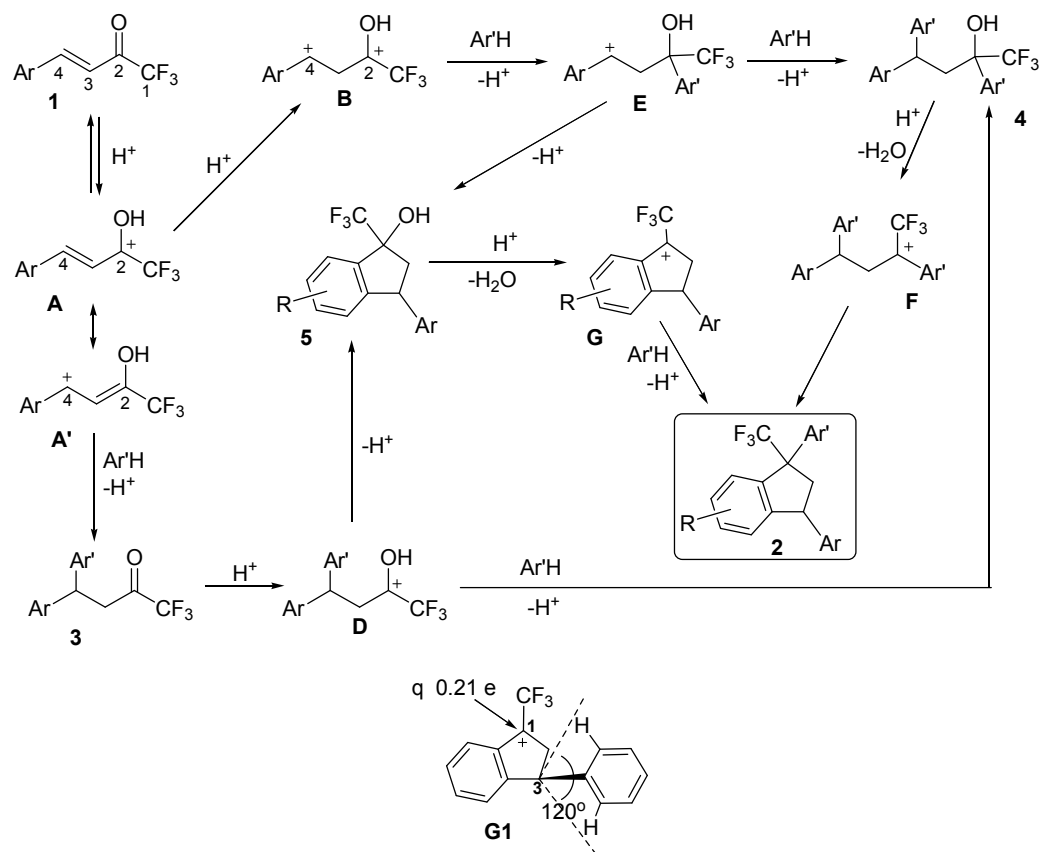
Scheme 4. Possible mechanism of the transformation of CF$_3$-enones **1** into indanes **2**. DFT

calculations of parameters of cation **G1**.

In order to validate the abovementioned mechanistic interpretation, we synthesized compounds

3c, **5a**, **4a**, **6a** (see their synthesis and X-ray structure of **13** in SI) all of which can be implicated as

intermediates on route from **1** to **2**, and exposed them in TfOH with excess of benzene (Scheme 5).

The reaction of diarylbutanone **3c** with benzene under activation with triflic acid gave indane **2a**

in high yield. Analogously compound **3b** afforded **2l** (Scheme 3). Indanol **5a** can also be transformed

into **2a** in the same conditions in 79 % yield. Interestingly, while alkenol **6a** had not initially been

thought to be an intermediate in the proposed mechanistic rationale (Scheme 5), we also found it to

give rise to **2a** under the reaction conditions. However, isolation of diarylbutanones **3** under lower

temperature indicates that this route to the final indanes is most probable, therefore participation of **6a**

can be discussed as a minor reaction route. In contrast, compound **4a** was not transformed into indane

**2a** (Scheme 5), making us question its involvement in the above transformations**.**
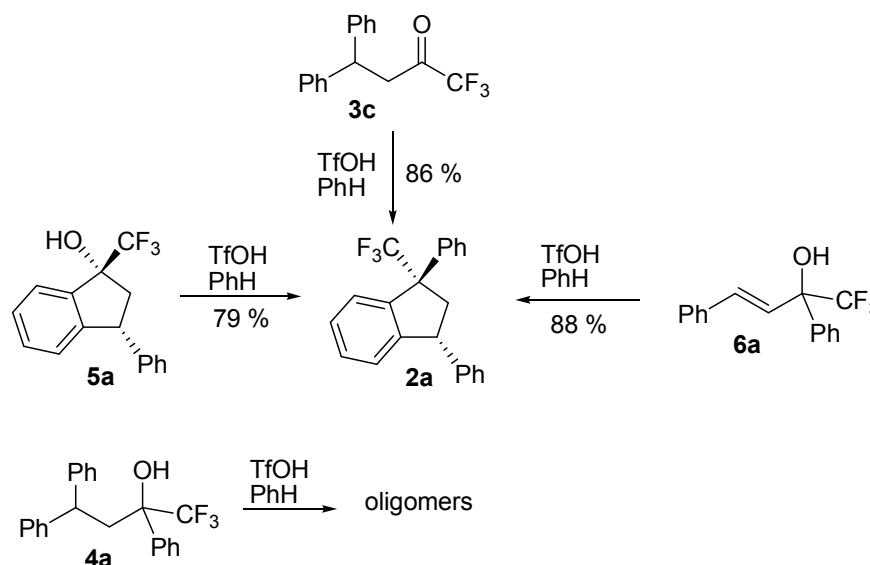
Scheme 5. Transformations of compounds **3c**, **5a**, **4a**, **6a** with benzene in TfOH (20 °C, 10 min.)

Thus, there are two most likely reaction pathways: 1) through cation **A** to structures **3, D, 5, G**,

and **2**; or 2) through cation **B** to structures **E, 5, G,** and **2**. Cation **G** is one of the key intermediates of

this reaction for both pathways. The addition of an aromatic molecule to the latter leads to *trans*-

orientation of the bulky aromatic groups, probably due to steric reasons. DFT calculation of charge

distribution in cation **G1** and its geometry was done (see SI). Large positive charge (0.21 e) is

localized on reactive center C^1 of indane system (Scheme 4). Geometry of this species exhibits that

cone angle with the apex at atom C^3 and ortho-protons of phenyl ring is around 120° (Scheme 4),

revealing rather great steric restriction for attack of arene molecule from this side of indane plane.

Apart from that, DFT calculations have shown that difference between the Gibbs energies of cis- and

trans-isomers **2a** is 1.1 kcal/mol in favor of the *trans*-isomer (see SI).

Concerning mechanisms of superelectrophilic activation of conjugated enones, in 1990s Shudo

and Ohwada[12a,b] postulated formation of reactive O,O-diprotonated at carbonyl oxygen species, which

may lie on reaction pathways. One may not exclude the participation of the dications in reactions, but

up to the moment these species have not been yet detected by NMR or other physical methods,

contrary to reliably characterized O,C-diprotonated forms of enones.[12f,q-t]

Additionally we observed two unusual reaction for CF_3-enones **1f** and **1g**. In both cases, the

formation of indane **2a** was observed (Scheme 6). That means that an exchange of *p*-anisyl (for **1f**) or

n-BuO (for **1g**) substituents takes place under superacidic reaction conditions. In the case of

buthoxyenone the transformation to **1a** takes place and some examples of similar transformations CF_3-

enones are known in literature.[1h,16] However, it is more difficult to explain the results of reaction with

1f. It is clear that electrophilic substitution with removal of anisole (good electrofuge) takes place.

However, it is most probable that the enone **1a** is not the major intermediate of the reaction because a

mixture of *cis*- and *trans*- indanes **2a** is formed. In addition, substitution of anisole may take place

from the initially formed indane structure.
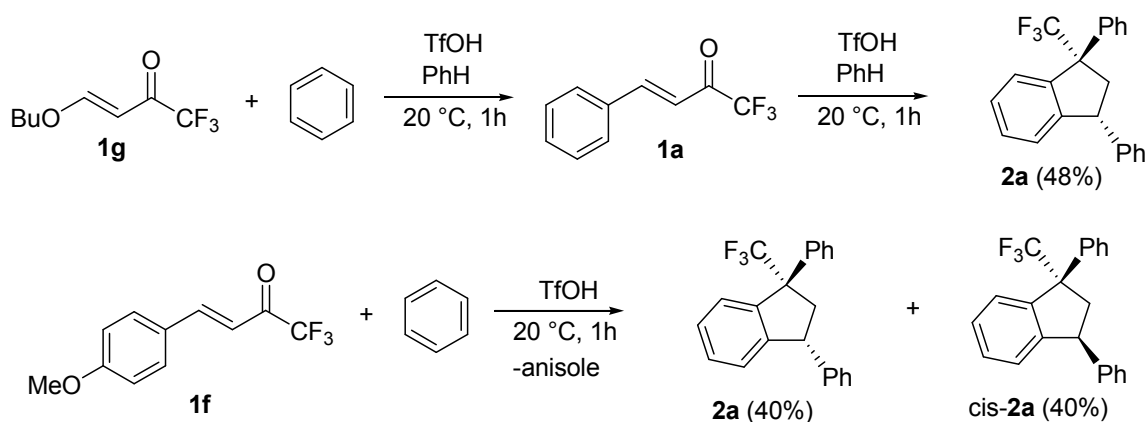
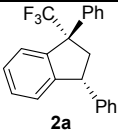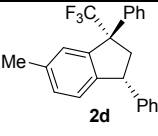**Scheme 6.** Reactions of compounds **1f**, **1g** with benzene in TfOH
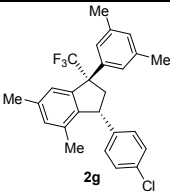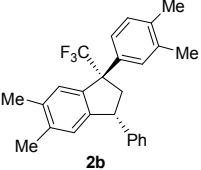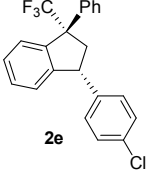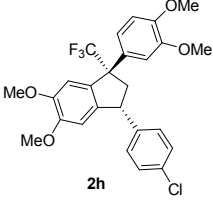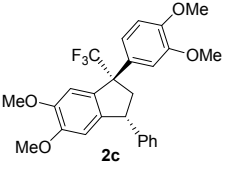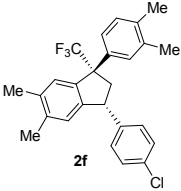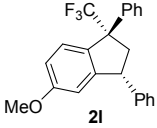
Summarizing the discussion of reaction mechanism, one may conclude that both O-protonated **A**

and O,C-diprotonated **B** species take part in the reactions of **1** with arenes in superacids. The

electrophilicity of these cations as well as its match to the electron-donating properties of the arenes

defines the outcome of the reaction. Strongly electrophilic cations **A** react even with poorly

nucleophilic arenes, such as benzene. On the other hand, cations **A**, having moderate electrophilicity,

react primarily with electron-rich arenes (xylenes, veratrol, etc.). Dications **B** are highly reactive superelectrophiles, reacting with all aromatic substrates. In some cases this reaction may proceed through mixed mechanisms with participation of both cations **A** and **B**.

Effects of 1,3-diaryl-1-trifluoromethyl indanes on the endocannabinoid system

The new *trans*-1,3-diaryl-1-trifluoromethyl indanes **2a-h,l**, which we succeeded obtaining as individual substances in this work, are distinctly lipophilic compounds (Table 2). With the aim of investigating the biological effects of this newly conceived scaffold, we assessed the binding properties of these compounds on cannabinoid receptors, which are the target of endogenous molecules called endocannabinoids that are also distinctly lipophilic.

Table 2. cLogP values calculated (using ACD/Labs 6.00 software) for *trans*-1,3-diaryl-1-trifluoromethyl indanes synthesized in this work.

Compound	cLogP value	Compound	cLogP value	Compound	cLogP value
2a	6.16 ± 0.64	**2d**	6.62 ± 0.65	**2g**	8.60 ± 0.66
2b	8.00 ± 0.65	**2e**	6.76 ± 0.65	**2h**	6.23 ± 0.70
2c	5.64 ± 0.69	**2f**	8.60 ± 0.66	**2l**	6.08 ± 0.65

The highly lipophilic *N*-arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG) are the most abundant and well-studied endocannabinoids and exert their biological activity primarily by binding to type-1 (CB_1) and type-2 (CB_2) cannabinoid receptors.[17] Most of the non-endogenous ligands for CB_1 and CB_2 are also characterized by high lipophilicity, as for example the phytocannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC) and the synthetic non-classical cannabinoids - SR141716A,[18] JWH015[19] and LY320135[20] (Figure 5). It is the lipophilic nature of *trans*-1,3-diaryl-1-trifluoromethyl indanes and the obvious similarity with the above synthetic cannabinoids (in terms of the arrangement of the aromatic periphery – *vide infra*) further supported our hypothesis of investigating the potential binding affinity of these molecules toward cannabinoid receptors.
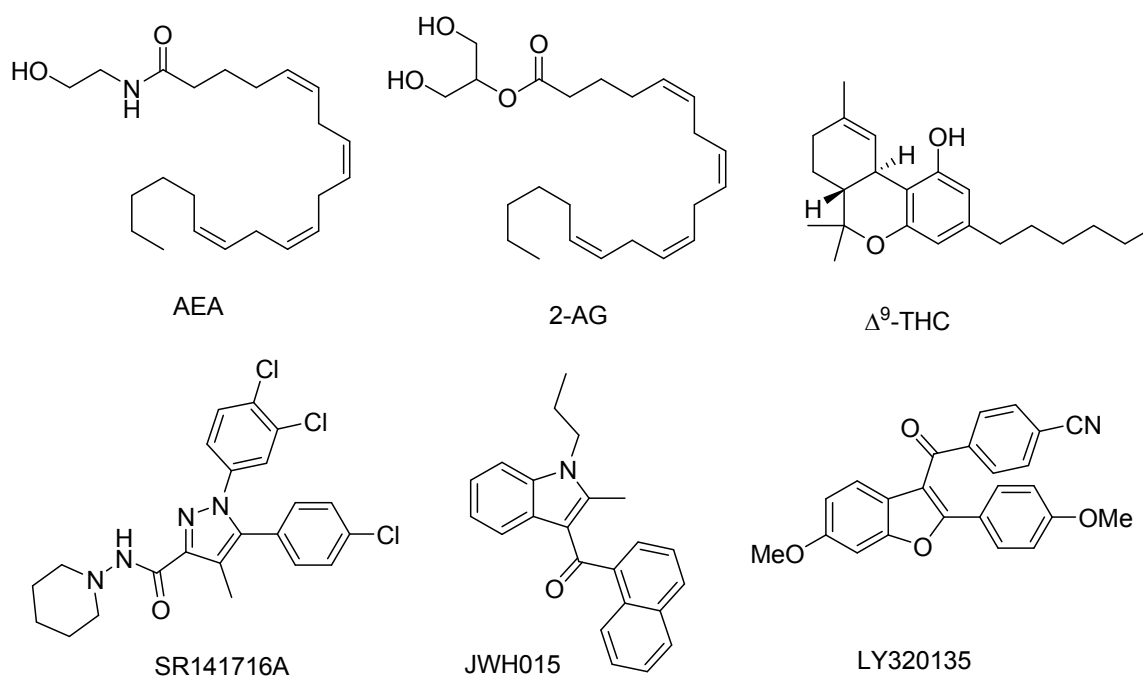

Figure 5. Endogenous (AEA and 2-AG) and natural (Δ^9-THC) and synthetic (SR141716A, JWH015 and LY320135) cannabinoid receptor ligands

Eight compounds **2a**, **2c**, **2d-h,l** were screened for their ability to displace [^{3}H]CP55,940 (the radiolabelled analogue of CP55,940, a potent, non-selective classical CB_1 and CB_2 ligand[21]) from CB_1

and CB_2 receptors. To our delight, three compounds (**2c**, **2e** and **2h**) showed a significant (higher than 50%) displacement of [³H]CP55,940 at the screening concentration of 1 μM. In addition, none of these compounds showed significant cytotoxicity at the concentration of 10 μM after 72 hours of incubation with SHSY5Y human neuroblastoma cells (Figure 6). Compound **2b** was insoluble under the assay conditions and could not be tested.
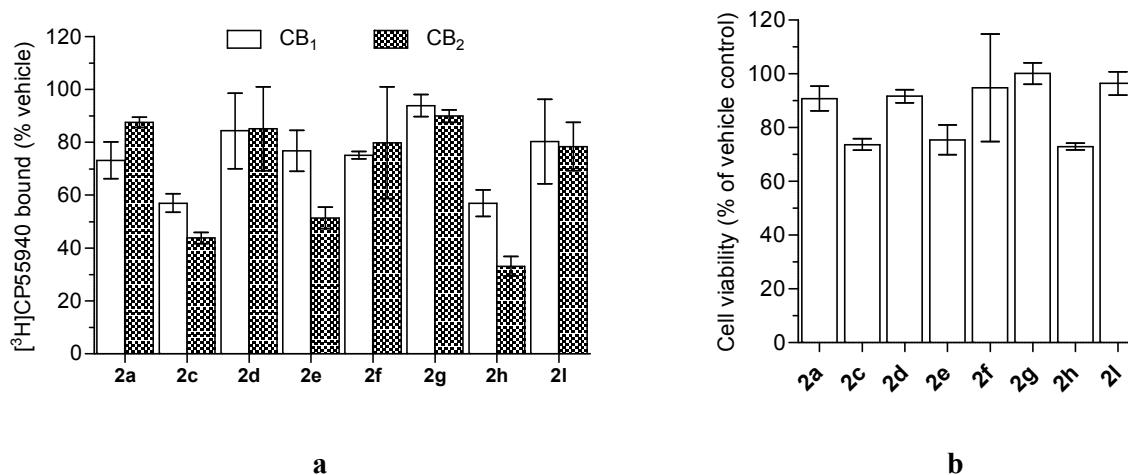
Figure 6 (a) Binding properties of compound **2a**, **2c**, **2d-h,l** tested at the concentration of 1 μM to CB_1 and CB_2 receptors (N = 3: n = 6, data shown are mean ± standard deviation); (b) cytotoxicity of the same compounds tested at 10 μM on SHSY5Y cells (SRB method,[22] 72 hours of incubation N = 2-3: n = 4-6, data shown are mean ± standard deviation).

The binding properties of compound

Compounds **2c**, **2e** and **2h** were further investigated by generating full concentration-dependent curves (Figure 7). All three compounds showed total displacement of the radioligand [³H]CP55,940 to both cannabinoid receptors with the most potent compound (**2h**) displaying a Ki value (calculated applying the Cheng-Prusoff equation) of 120 nM towards CB_2 receptor and a 6-fold selectivity *vs*. CB_1 receptor (Ki value of 750 nM) (Figure 7). The highest affinity shown by compound **2h** could be explained by an interaction with the receptor similar to other non-classical synthetic cannabinoids (SR141716A (rimonabant), JWH015 and LY320135 shown in Figure 4), considering quite an effective

spatial overlay of **2h** with these three known CB_1/CB_2 ligands, especially with LY320135, suggesting potentially similar functional signaling by our *trans*-diaryl indanes (Figure 8).[23]
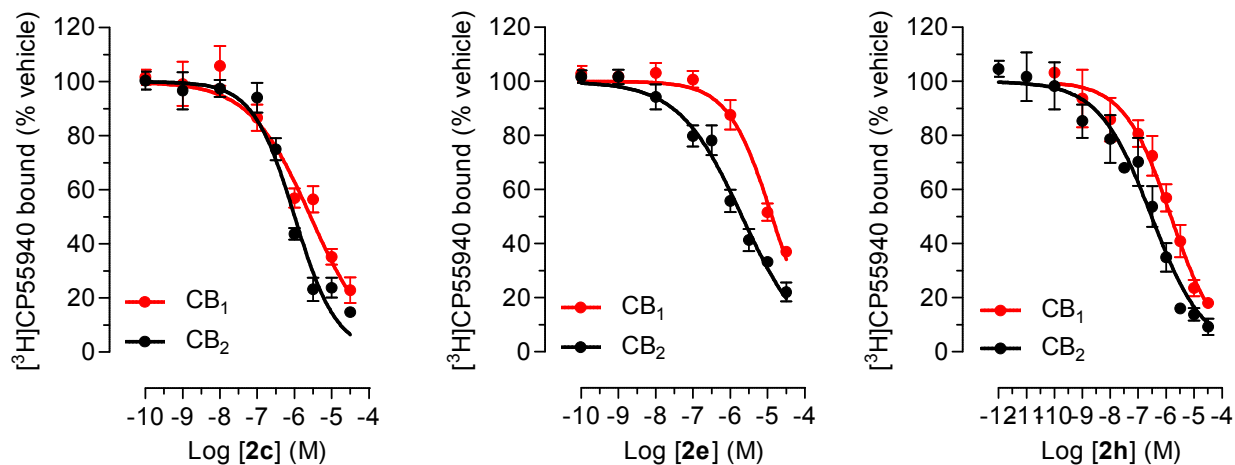
	Ki value (mean and 95%, CI) µM	
	*h***CB₁**	*h***CB₂**
2c	1.35 (0.91-2.05)	0.55 (0.42-0.73)
2e	6.55 (4.92-8.71)	1.19 (0.75-1.68)
2h	0.75 (0.48-1.15)	0.12 (0.07-0.20)

Figure 7. Concentration-dependent binding curves and Ki values calculated for compounds **2c**, **2e** and **2h** (N = 3-6: n = 9-18, data shown are mean ± standard deviation for the binding curves and mean and 95% confidence interval for Ki values)
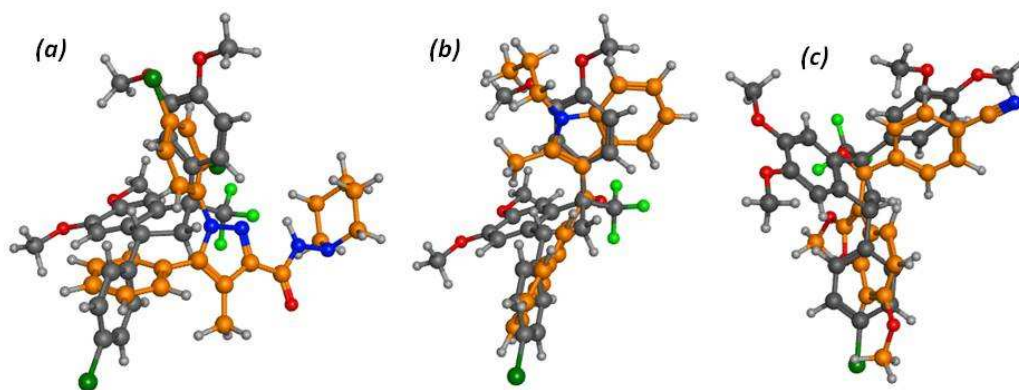
Figure 8. Spatial overlay of the structure of compound **2h** (shown in grey) with *(a)* SR141716A, *(b)* JWH015 and *(c)* LY320135 – all shown in orange.

The trifluoromethyl indanes **2a**, **2c** and **2d-h,l** were also tested for potential inhibition of the key components of the endocannabinoid system such as the hydrolytic enzymes fatty acid amide hydrolase (FAAH) for AEA and monoacylglycerol lipase (MAGL) and α/β hydrolase domain (ABHDs) for 2-AG, the oxidative enzyme cyclooxygenase-2 for 2-AG and arachidonic acid and the putative endocannabinoid membrane transporter.[24] Interestingly, the compounds showed negligible effects on all these targets (see SI), clearly indicating that **2c**, **2e** and **2h** selectively bind to cannabinoid receptors, particularly CB_2 receptors which are a highly promising pharmacological target for treating inflammatory and neuropathic pain[25] and neurodegenerative diseases.[26]

Conclusions

Novel efficient stereoselective synthesis of *trans*-1,3-diaryl-1-trifluoromethyl indanes was developed on the basis of superelectrophilic activation of 4-aryl-1,1,1-trufluorobut-3-en-2-ones and subsequent reaction with arenes. The reaction intermediates, O-protonated and O,C-diprotonated forms of 4-aryl-1,1,1-trufluorobut-3-en-2-ones have been studied by ^{1}H, ^{13}C, ^{19}F NMR, and DFT calculations. Both of these cations take part in the reaction, depending on electrophilicity of the cations and electron donating properties of arenes.

Among the novel *trans*-1,3-diaryl-1-trifluoromethyl indanes obtained in this work, three moderately potent ligands of cannabinoid receptors have been identified. The most potent compound (**2h**) displayed a 120 nM affinity toward CB_2 receptor and a 6-fold selectivity *vs.* CB_1 receptor. In the absence of cytotoxicity and any effect on the other key components of the endocannabinoid system, the new *trans*-1,3-diaryl-1-trifluoromethyl indane scaffold clearly has a value for the design on selective modulators of cannabinoid (in particular, CB_2) receptors.

Experimental

The NMR spectra of solutions of compounds in $CDCl_3$ were recorded on Bruker AVANCE III 400 (at 400, 376 and 100 MHz for ^1H, ^{19}F and ^{13}C NMR spectra respectively) or Bruker DPX 300 (at 300 and 75 MHz for ^1H and ^{13}C NMR spectra respectively) spectrometers at 25 °C. The residual proton-solvent peak $CDCl_3$ (δ 7.26 ppm) for ^1H NMR spectra and the carbon signal of $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR spectra were used as references. NMR experiments in the superacids TfOH or FSO_3H were performed on Bruker AVANCE III spectrometer (at 500, 476 and 125 MHz for ^1H, ^{19}F and ^{13}C NMR spectra respectively). NMR spectra in superacids were referenced to the signal of CH_2Cl_2 added as internal standard: δ 5.32 ppm for ^1H NMR spectra, and δ 53.84 ppm for ^{13}C NMR spectra. HRMS was carried out at instruments Bruker maXis HRMS-ESI-QTOF and Varian 902-MS MALDI Mass Spectrometer. Chromato-mass-spectrometry data were obtained at Shimadzu QP-2010 Ultra with a SPB-1 SULFUR capillary column (30 m × 0.32 mm), thickness of the stationary phase 1.25 μm. The preparative reactions were monitored by thin-layer chromatography carried out on silica gel plates (Alugram SIL G/UV-254), using UV light for detection. Preparative column chromatography was performed on silica gel 60 Merck with hexanes-ethyl acetate mixture eluation.

For single crystal X-ray diffraction experiments, crystals of all compounds were fixed on a micro mount and placed on a Agilent Technologies Excalibur Eos diffractometer using monochromated Mo*Kα* radiation (**2a**, **2b**) and Agilent Technologies SuperNova using monochromated Cu*Kα* (**2e**, **2g**, **2h**) (Oxford Diffraction) diffractometer and measured at a temperature of 100K. The structures have

been solved by the direct methods SHELXS and refined for unique reflections with $|F_o| \geq 4\sigma_F$ by means of the SHELXL program[27] incorporated in the *OLEX2* program package.[28] The carbon-bound H atoms were placed in calculated positions and were included in the refinement in the 'riding' model approximation, with $U_{iso}(H)$ set to $1.5U_{eq}(C)$ and C–H 0.96 Å for the CH_3 groups, $U_{iso}(H)$ set to $1.2U_{eq}(C)$ and C–H 0.97 Å for the CH_2 groups, $U_{iso}(H)$ set to $1.2U_{eq}(C)$ and C–H 0.93 Å for the CH groups. CCDC 1047066 – (**2a**), CCDC 1047331 – (**2b**), CCDC 1047468 – (**2e**), CCDC 1047315 – (**2g**), CCDC 1047593 – (**2h**) contain the supplementary crystallographic data, which can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk.

All computations has been carried out at the DFT/HF hybrid level of theory using Becke's three-parameter hybrid exchange functional in combination with the gradient-corrected correlation functional of Lee, Yang, and Parr (B3LYP) by using GAUSSIAN 2003 program packages[29] The geometries optimization were performed using the 6-311+G(2d,2p) basis set The Hessian matrix was calculated analytically for the optimized structures in order to prove the location of correct minima (no imaginary frequencies) and to estimate the thermodynamic parameters. Enthalpies and Gibbs free energies were calculated for 25°C.

Starting 4-aryl-1,1,1-trufluorobut-3-en-2-ones 1a-i were prepared according to the literature procedures.[1b,f-h]

General procedure for reaction of compounds 1a-g with arenes in superacids CF_3SO_3H or FSO_3H. Synthesis of compounds 2a-n, cis-2a, 3a,b.

CF_3-enone **1a-g** (0.23 mmol) was added to mixture of TfOH (at 20 °C) (1-2 mL) or FSO_3H (at -80…-60 °C) (1 mL, co-solvents SO_2 or CH_2Cl_2) with benzene (0.3 ml) or another arene (1 mmol). Reaction mixture was magnetically stirred for 1-2 h. Then in case of TfOH the mixture was poured into ice water (30 mL) and extracted with chloroform (2×40 mL). The extracts were combined, washed with water, a saturated aqueous solution of $NaHCO_3$, water again, and dried over Na_2SO_4. The solvent

was distilled off under reduced pressure, and the residue was recrystallized from methanol or subjected to chromatographic separation on silica gel using hexanes-ethyl acetate mixtures (20:1 to 10:1) as an eluent. For FSO$_3$H the reaction mixture was quenched with frozen at -80 °C concentrated aqueous HCl (10 mL), diluted with water (20 ml), then extracted and worked up as described above. Yields of the obtained compounds are given in Table 1 and Schemes 2, 3, 6.

(1*RS*,3*RS*)-1-Trifluoromethyl-1,3-diphenylindane (2a). Yield 65 mg, 84%. Colorless solid, mp 106-108°C (MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.80 (dd, *J* = 11.2 Hz, 12.5 Hz, 1H), 3.05 (dd, *J* = 6.8 Hz, 12.5 Hz, 1H), 4.09 (dd, *J* = 11.2 Hz, 6.8 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 6.8 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.25-7.38 (m, 8H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.64 (d, 1H, *J* = 7.9 Hz).^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 46.9 (CH), 48.3 (CH$_2$), 60.8 (q, <u>C</u>-CF$_3$, *J* = 26.4 Hz), 125.7, 125.9 (d, *J* = 1.3 Hz), 127.17, 127.20, 127.6 (q, CF$_3$, *J* = 281.5 Hz), 128.0, 128.5, 128.6 (2CH), 128.8, 129.0, 137.5, 140.7 (d, *J* = 1.4 Hz), 142.8, 147.5. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69.16 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 338 *M*$^+$ (3), 260 (100), 191 (50). HRMS: C$_{22}$H$_{17}$F$_3$ found 338.1285 *M*+; calcd. 338.1282.

(1*SR*,3*RS*)-1-Trifluoromethyl-1,3-diphenylindane (cis-2a). Obtained as 1:1 mixture with indane **2a.** Yield 25 mg, 80%. ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.52 (dd, *J* = 8.4 Hz, 14.4 Hz, 1H), 3.43 (dd, *J* = 8.4 Hz, 14.4 Hz, 1H), 4.63 (t, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 7.1 Hz, 2H), 7.20-7.24 (m, 1H), 7.25-7.35 (m, 8H), 7.47 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 48.1 (CH$_2$), 49.9 (CH), 61.7 (q, <u>C</u>-CF$_3$, *J* = 25.3 Hz), 127.6 (q, CF$_3$, *J* = 281 Hz), 141.2, 141.51, 141.52, 144.4, 148.4. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69.36 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 338 M$^+$ (100), 269 (100), 260 (90), 191 (100). HRMS: C$_{22}$H$_{17}$F$_3$ found 338.1285 *M*+; calcd. 338.1282.

(1*RS*,3*RS*)-1-Trifluoromethyl-5,6-dimethyl-1-(3,4-dimethylphenyl)-3-phenylindane (2b). Yield 80 mg, 77%. Colorless solid, mp 106-108°C (MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz) δ, ppm: 2.25 (s, 3H, CH$_3$), 2.28 (s, 6H, 2CH$_3$), 2.38 (s, 3H, CH$_3$), 2.74 (dd, 1H, *J* = 12.5 Hz, 11 Hz), 3.00 (dd, 1H, *J* = 6.5 Hz, 12.5 Hz), 4.06 (dd, 1H, *J* = 6.5 Hz, 11 Hz), 6.72 (s, 1H), 7.01-7.12 (m, 2H), 7.17 (s,

1H), 7.22-7.25 (m, 2H), 7.29-7.36 (m, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ, ppm: 19.3 (CH$_3$), 19.9 (CH$_3$), 20.1 (CH$_3$), 47.0 (CH$_2$), 47.8 (CH), 60.1 (q, C-CF$_3$, J = 25 Hz), 125.8, 126.0, 126.3, 126.5, 126.8, 128.5, 128.6, 129.5, 129.55, 129.6 (q, CF$_3$, J = 275 Hz), 135.2, 135.3, 136.2, 136.4, 138.4, 143.2, 144.8. ^{19}F NMR (CDCl$_3$, 470 MHz) δ, ppm: -69.19 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 394 (5) [M]$^+$, 325 (30), 289 (100), 219 (34). HRMS: C$_{26}$H$_{25}$F$_3$ found 394.1911 M+; calcd. 394.1908.

(1RS,3RS)-1-Trifluoromethyl-5,6-dimetoxy-1-(3,4-dimetoxyphenyl)-3-phenylindane (**2c**). Yield 77 mg, 75%. Colorless solid, mp 104-108°C (MeOH). ^{1}H NMR (CDCl$_3$, 500 MHz) δ, ppm: 2.68 (dd, 1H, J = 11 Hz, 12.5 Hz), 2.90 (dd, 1H, 12.5 Hz, 7 Hz), 3.72 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 4.04 (dd, 1H, J = 7 Hz, 11 Hz), 6.40 (s, 1H), 6.70-6.78 (m, 2H), 6.88 (s, 1H), 7.03 (s, 1H), 7.18 (d, 2H, J = 7 Hz), 7.22-7.25 (m, 1H), 7.31 (t, 2H, J = 7.4 Hz). ^{13}C NMR (CDCl$_3$, 125 MHz) δ, ppm: 47.8 (CH$_2$), 48.2 (CH), 55.82 (OMe), 55.83 (OMe), 56.0 (OMe), 56.3 (OMe), 60.2 (q, C-CF$_3$, J = 26 Hz), 107.9, 108.1, 110.6, 111.7, 121.0, 127.0, 128.4, 128.7, 128.8, 130.5, 132.4, 133.4 (q, CF$_3$, J = 275 Hz), 139.6, 143.1, 148.56, 148.62 (2C), 150.0. ^{19}F NMR (CDCl$_3$, 470 MHz) δ, ppm: -69.22 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 458 M$^+$ (32), 389 (33), 320 (100). HRMS: C$_{26}$H$_{25}$F$_3$O$_4$ found 458.1708 M+; calcd. 458.1705.

(1RS,3RS)-1-Trifluoromethyl-6-methyl-1,3-diphenylindane (**2d**). Yield 31 mg, 35%. Colorless solid, mp 102-105°C (MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.38 (s, 3H, CH$_3$), 2.68 (dd, 1H, J = 12.5 Hz, 11 Hz), 2.93 (dd, 1H, J = 6.8 Hz, 12.5 Hz), 3.96 (dd, 1H, J = 6.8 Hz, 11 Hz), 6.75 (d, 1H, J = 7.8 Hz), 7.07 (d, 1H, J = 7.8 Hz), 7.11-7.14 (m, 9H), 7.18 (s, 1H), 7.34 (s, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 21.7 (CH$_3$), 47.2 (CH$_2$), 47.9 (CH), 60.8 (q, C-CF$_3$, J = 29 Hz), 124.7, 125.4, 126.3 (q, CHCCCF$_3$, J = 1.1 Hz), 127.1, 128.0, 128.5, 128.5 (q, CF$_3$, J = 256 Hz), 128.6 (2CH), 128.8, 129.8, 137.0, 137.7, 140.8, 143.1, 144.6. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69,01 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 352 M$^+$ (15), 274 (100), 205 (40). HRMS: C$_{23}$H$_{19}$F$_3$ found 352.1441 M+; calcd. 352.1439.

(1RS,3RS)-3-(4-Chlorophenyl)-1-trifluoromethyl-1-phenylindane (**2e**). Yield 53 mg, 80%. Colorless solid, mp 109-112°C (MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.72 (dd, 1H, J = 12.5

Hz, 11.2 Hz), 3.03 (dd, 1H, J = 12.5 Hz, 6.8 Hz), 4.06 (dd, 1H, J = 11.2 Hz, 6.8 Hz), 6.93 (d, 1H, J = 7.6 Hz), 7.14 (d, 2H, J = 8.4 Hz), 7.36-7.28 (m, 8H), 7.40 (t, 1H, J = 7.5 Hz), 7.63 (d, 1H, J = 7.6 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 46.9 (q, CH$_2$, J = 1.3 Hz), 47.7 (CH), 60.8 (q, $\underline{C}$-CF$_3$, J = 25 Hz), 125.5, 126.0 (J 1.2 Hz), 127.4, 127.6 (q, CF$_3$, J = 281 Hz), 128.1, 128.5, 128.6 (q, J = 0.8 Hz), 129.0, 129.9, 133.0, 137.3, 140.7 (q, J = 1.3 Hz), 141.9, 147.0. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69.19 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 372 M$^+$ (15), 337 (15), 303 (10), 294 (100). HRMS: C$_{22}$H$_{16}$F$_3$Cl found 372.0893 M+; calcd. 372.0893.

(1RS,3RS)-3-(4-Chlorophenyl)-1-trifluoromethyl-5,6-dimethyl-1-(3,4-dimethylphenyl) indane (2f). Yield   50 mg, 57%. Colorless solid, mp 113-115°C (MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz) δ, ppm: 2.23 (s, 3H, CH$_3$), 2.25 (s, 6H, 2CH$_3$), 2.36 (s, 3H, CH$_3$), 2.65 (dd, 1H, J = 12.4 Hz, 10.6 Hz), 2,96 (dd, 1H, J = 10.6 Hz, 6.5 Hz), 4.02 (dd, 1H, J = 6.5 Hz, 10.6 Hz), 6.67 (s, 1H), 7.00 (d, 1H, J = 8.0 Hz), 7.07 (d, 1H, J = 8.0 Hz), 7.14 (m, 3H), 7.30 (d, 2H, J = 8.4 Hz), 7.36 br (s, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 19.5 (CH$_3$), 20.1 (2CH$_3$), 20.3 (CH$_3$), 47.2 (d, CH$_2$, J = 0.8 Hz), 47.4 (CH), 60.3 (q, $\underline{C}$-CF$_3$, J = 26.2 Hz), 126.1, 126.3 (d, J = 4.9 Hz), 126.8 (d, J = 0.7 Hz), 127.8 (q, CF$_3$, J = 282 Hz), 128.9, 126.8, 129.6, 130.0, 132.7, 135.1, 135.8, 136.46, 136.63, 137.5, 141.9, 144.5. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69.22 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 428 M$^+$ (10), 359 (7), 322 (100), 253 (12). HRMS: C$_{26}$H$_{24}$F$_3$Cl found 428.1514 M+; calcd. 428.1519.

(1RS,3RS)-3-(4-Chlorophenyl)-1-trifluoromethyl-4,6-dimethyl-1-(3,5-dimethylphenyl) indane (2g). Yield 46 mg, 54%. Colorless solid, mp 103-105°C (MeOH). ^{1}H NMR (CDCl$_3$, 300 MHz) δ, ppm: 1.71 (s, 3H, CH$_3$), 2.27 (s, 6H, 2CH$_3$), 2.41 (s, 3H, CH$_3$), 2.60 (dd, 1H, J = 13.2 Hz, 9.8 Hz), 3.01 (dd, 1H, J = 13.2 Hz, 7.6 Hz), 4.15 (t, 1H, J = 8.6 Hz), 6.85 (s, 2H), 6.96 (s, 1H), 6.97 (s, 1H), 7.08 (d, 2H, J = 8.2 Hz), 7.22 (s, 1H), 7.27 (d, 1H, J = 8.2 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 19.9 (CH$_3$), 21.5 (CH$_3$), 21.7 (2CH$_3$), 47.5 (CH), 48.0 (d, CH$_2$, J = 1 Hz), 60.7 (q, $\underline{C}$-CF$_3$, J = 26.2 Hz), 124.3 (d, J = 1.1 Hz), 126.0 (d, J = 0.9 Hz), 127.8 (q, CF$_3$, J = 282 Hz), 129.0, 129.4, 129.6, 132.0, 132.3, 135.3, 137.5, 137.8, 138.8, 141.3, 141.58, 141.59, 143.5. ^{19}F NMR (CDCl$_3$, 376 MHz) δ,

ppm: -68.72 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 428 [M]$^+$ (30), 359 (15), 322 (100), 253 (20).

HRMS: C$_{26}$H$_{24}$F$_3$Cl found 428.1517 *M*+; calcd. 428.1519.

(1*RS*,3*RS*)-3-(4-Chlorophenyl)-1-trifluoromethyl-5,6-dimethoxy-1-(3,4-dimethoxyphenyl)

indane (**2h**). Yield 64 mg, 73%. Colorless solid, mp 111-114°C (MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz)

δ, ppm: 2.65 (dd, 1H, *J* = 12.6 Hz, 10.6 Hz), 2.91 (dd, 1H, *J* = 12.6 Hz, 6.9 Hz), 3.77 (s, 3H, OCH$_3$),

3.80 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 3.94 (s, 3H, OCH$_3$), 4.05 (dd, 1H, *J* = 10.6 Hz, 6.8 Hz), 6.38

(s, 1H, H), 6,73 (dd, 1H, *J* = 8.5 Hz, 1.8 Hz), 6.88 (d, 1H, *J* = 8.5 Hz), 6.89 (d, 1H, *J* = 1.8 Hz), 7.05

(s, 1H), 7.14 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 47.7

(CH), 48.0 (CH$_2$), 55.97 (OMe), 55.99 (OMe), 56.12 (OMe), 56.40 (OMe), 60.4 (q, $\underline{C}$-CF$_3$, *J* = 26.3

Hz), 107.8, 108.3 (d, *J* = 0.8 Hz), 110.7, 111.8, 121.1, 127.7 (q, CF$_3$, *J* = 282 Hz), 129.4, 129.9, 130.5,

132.5, 132.9, 139.2, 141.8, 148.8 (q, *J* = 4.1 Hz), 150.3. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69.25

(s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 492 [M]$^+$ (50), 423 (40), 354 (100). HRMS: C$_{26}$H$_{24}$F$_3$O$_4$Cl

found 492.1318 *M*+; calcd. 492.1315.

(1*RS*,3*RS*)-1-Trifluoromethyl-5-methoxy-1,3-diphenylindane (**2i**). Yield 11 mg, 76%.

Colorless solid, mp 102-104°C (MeOH). ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.79 (t, 1H, *J* = 12.5

Hz), 3.01 (dd, 1H, *J* = 12.5 Hz, 11 Hz), 3.74 (3H, OMe), 4.03 (dd, 1H, *J* = 11 Hz, 12.5 Hz), 6.45 (d,

1H, *J* = 2.4 Hz), 6.93 (dd, 1H, *J* = 8.4 Hz, 2.4 Hz), 7.19-7.23 (m, 2H), 7.28 (d, 1H, *J* = 7.1 Hz), 7.30-

7.36 (m, 7H), 7.51 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 47.3 (CH$_2$), 48.4 (CH),

55.6 (OMe), 60.2 (q, $\underline{C}$-CF$_3$, *J* = 29.5 Hz), 110.6, 113.5, 126.6 (q, $\underline{CH}$CCCF$_3$, *J* = 1 Hz), 127.2, 127.7

(q, CF$_3$, *J* = 282 Hz), 128.0, 128.4, 128.6 (d, *J* = 0.8 Hz), 128.7, 128.9, 132.8, 138.0, 142.7, 149.2,

160.6. ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -69,46 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 368 M$^+$

(80), 299 (100), 290 (25), 221 (30). HRMS: C$_{23}$H$_{19}$F$_3$O found 368.1385 *M*+; calcd. 368.1388.

1,1,1-Trifluoro-4-(4-methylphenyl)-4-(thiophen-2-yl)butan-2-one (**3a**). Yield 44 mg, 77%.

Yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 2.32 (s, 3H, OMe), 3.40-3.52 (m, 2H, AB-system,

CH$_2$), 4.86 (t, 1H, CH, *J* = 7.3 Hz), 6.83 (d, 1H, *J* = 3.5 Hz), 6.91 (dd, 1H, *J* = 5 Hz, 3.5 Hz), 7.10-

7.19 (m, 5H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 21.2 (CH$_3$), 40.0 (CH), 44.0 (CH$_2$), 115.5 (CF$_3$, *J*

= 292 Hz), 124.40, 124.27, 126.9, 127.4, 129.7, 137.2, 139.3, 146.9, 189.0 (q, <u>C</u>OCF$_3$, J = 35.7 Hz). ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -79.39 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 298 M$^+$ (20), 283 [M-CH$_3$]$^+$ (15), 229 [M-CF$_3$]$^+$ (7), 187 [M-CH$_2$COCF$_3$]$^+$ (100).   HRMS: C$_{14}$H$_{13}$F$_3$OS found 286.0640 M+; calcd. 286.0640.

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-phenylbutan-2-one (3b). Yield 44 mg, 68%. Colorless oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ, ppm: 3,48 (d, 2H, CH$_2$, J = 7.5 Hz), 3.77 (s, 3H, OMe), 4.63 (t, 1H, CH, J = 7.5 Hz), 6.73-6.77 (m, 2H), 6.82 (d, 1H, J = 7.8 Hz), 7.20-7.25 (m, 4H), 7.28-7.34 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ, ppm: 42.6 (CH$_2$), 44.7, 55.3, 109.8, 112.0, 115.6 (CF$_3$, J = 292 Hz), 117.5, 127.1, 127.6, 129.0, 130.0, 142.4, 144.2, 160.0, 189.4 (q, <u>C</u>OCF$_3$, J = 35.5 Hz). ^{19}F NMR (CDCl$_3$, 376 MHz) δ, ppm: -79.38 (s, CF$_3$). MS (GC-MS, EI), m/z, (I$_{rel.}$, %) – 308 M$^+$ (100), 239 (23), 197 (95). HRMS: C$_{17}$H$_{15}$F$_3$O$_2$ found 308.1021 M+; calcd. 308.1024.

Supporting information: Figures of ^{1}H, ^{13}C, ^{19}F NMR spectra, X-ray data of obtained compounds, additional biological profile of compounds **2a-h,l**, details of DFT calculations.

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Notes and references

1. a) S. G. K. Prakash, M. Mandal, S. Schweizer, N. A. Petasis, G. A. Olah, *Org. Lett.* 2000, **2***, 3173-3176; b) V. G. Nenajdenko, I. G. Gridnev, E. S. Balenkova, *Tetrahedron* 1994, **50**, 11023-11038; c) I. Ashworth, P. Hopes, D. Levin, I. Patel, R. Salloo, *Tetrahedron Lett.* 2002, **43**, 4931-4933; d) R. J. Andrew, J. M. Mellor, *Tetrahedron* 2000, **56**, 7261-7266; e) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* 2000, **122**, 11260-11261; f) V. G. Nenajdenko, A. L. Krasovskiy, E. S. Balenkova, *Tetrahedron* 2007, **63**, 12481-12539; g) V. G. Nenajdenko, I. F. Leshcheva, E. S. Balenkova, *Tetrahedron* 1994, **50**, 775-782; h) V. G. Nenajdenko, A. L. Krasovskiy, M. V. Lebedev, E. S. Balenkova, *Synlett* 1997, 1349-1350; i) V. G. Nenajdenko, A. V. Sanin, E. S. Balenkova, *Russ. Chem. Rev.* 1999, **68**, 437-458.

2. a) R. P. Singh, R. L. Kirchmeier, J. M. Shreeve, *Org. Lett.* 1999, **1**, 1047-1049; b) D. Zhang, C. Yuan, *Tetrahedron* 2008, **64**, 2480-2488; c) M. R. Bryce, M. A. Chalton, A. Chesney, D. Catterick, J. W. Yao, J. A. K. Howard, *Tetrahedron* 1998, **54**, 3919-3928; d) J.-N. Volle, M. Schlosser, *Eur. J. Org. Chem.* 2002, 1490-1492; e) A. Yu. Rulev, V. M. Muzalevskiy, E. V. Kondrashov, I. A. Ushakov, A. R. Romanov, V. G. Nenajdenko, *Org. Lett.* 2013, **15**, 2726-2729.

3. a) Z. Pei, Y. Zheng, J. Nie, J.-A. Ma, *Tetrahedron Lett.* 2010, **51**, 4658-4661; b) S. Sasaki, T. Yamauchi, K. Higashiyama, *Tetrahedron Lett.* 2010, **51**, 2326-2328; c) Y. Xin, J. Zhao, J. Han, S. Zhu, *J. Fluor. Chem.* 2010, **131**, 642-645; d) M. A. P. Martins, A. F. C. Flores, G. P. Bastos, N. Zanatta, H. G. Bonacorso, *J. Het. Chem.* 1999, **36**, 837-840; e) N. Zanata, D. M. Borchhardt, S. H. Alves, H. S. Coelho, A. M. C. Squzani, T. M. Marchi, H. G. Bonacorso, M. A. P. Martins, *Bioorg. Med. Chem. Lett.* 2006, **14**, 3174-3184.

4. a) V. J. Majo, J. Prabharkaran, N. R. Simpson, R. L. Van Heertum, J. J. Mann, J. S. D. Kumar, *Bioorg. Med. Chem. Lett.* 2005, **15,** 4268-4271; b) M. A. P. Martins, R. F. Blanco, C. M. P. Pereira, P. Beck, S. Brondani, W. Cunico, N. E. K. Zimmermann, H. G. Bonacorso, N. Zanatta, *J. Fluor. Chem.* 2002, **118**, 69-72; c) A. F. C. Flores, S. Brondani, L. Puzziti, M. A. P. Martins, N. Zanatta, H. G. Bonacorso, D. C. Flores, *Synthesis* 2005, **16**, 2744-2750; d) M. A. P. Martins, G. M. Siquera, G. P. Bastos, H. G. Bonacorso, N. Zanatta, *J. Het. Chem.* 1996, **33**, 1619-1622; e) P. Yeh, D. S. B. Daniels,

D. B. Cordes, A. M. Z. Slawin, A. D. Smith, *Org. Lett.* 2014, **16**, 964-967; f) K. Funabiki, A. Isomura, Y. Yamaguchi, W. Hashimoto, K. Matsunaga, K. Shibata, M. Matsui, *J. Chem. Soc. Perkin I* 2001, 2578-2582; g) K. Funabiki, H. Nakamura, M. Masaki, K. Shibata, *Synlett.* 1999, **6**, 756-758; h) H. G. Bonacorso, A. P. Wentz, N. Zanatta, M. A. P. Martins, *Synthesis* 2001, **5**, 1505-1508; i) N. Zanatta, D. C. Flores, C. C. Madruga, A. F. C. Flores, H. G. Bonacorso, M. A. P. Martins, *Synthesis* 2003, **6**, 894-898; j) H. G. Bonacorso, H. Lewandowski, R. L. Drekener, M. B. Costa, C. M. P. Pereira, A. D. Wastowski, C. Peppe, M. A. P. Martins, N. Zanatta, *J. Fluorine Chem.* 2003, **122**, 159-163; k) H. G. Bonacorso, I. S. Lopes, A. D. Wastowski, M. A. P. Martins, N. Zanatta, *J. Fluorine Chem.* 2003, **120**, 29-32.

5. a) T. Hiyama, Organofluorine Compounds. Chemistry and Applications; Springer: Berlin, 2000; b) R. D. Chambers, Fluorine in Organic Chemistry; Blackwell: Oxford, 2004; c) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications; Wiley-VCH: Weinheim, 2004; d) K. Uneyama, Organofluorine Chemistry; Blackwell: Oxford, 2006; e) G. Theodoridis, Fluorine-containing agrochemicals: An overview of recent developments, in A. Tressaud (Ed.), Advances in Fluorine Science, Vol. 2; Elsevier: Amsterdam, 2006, pp. 121-175; f) J. P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine; Wiley: Hoboken, 2008; g) A. Tressaud, G. Haufe (Eds), Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals; Elsevier: Amsterdam, 2008, pp. 553-778; h) A. Gakh, K. L. Kirk (Eds.), Fluorinated Heterocycles; Oxford University Press: Oxford, 2008; i) V. A. Petrov (Ed), Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications; Wiley: Hoboken, 2009; j) V. G. Nenajdenko (Ed.), Fluorine in Heterocyclic Chemistry; Springer: Berlin-Heidelberg, 2014.

6. a) H. M. H. Alkhafaji, D. S. Ryabukhin, V. M. Muzalevskiy, A. V. Vasilyev, G. K. Fukin, A. V. Shastin, V. G. Nenajdenko, *Eur. J. Org. Chem.* 2013, 1132-1143; b) H. M. H. Alkhafaji, D. S. Ryabukhin, V. M. Muzalevskiy, L. V. Osetrova, A. V. Vasilyev, V. G. Nenajdenko, *Russ. J. Org. Chem.* 2013, **49**, 327-341.

7. A. N. Kazakova, R. O. Iakovenko, V. M. Muzalevskiy, I. A. Boyarskaya, M. S. Avdontceva, G. L. Starova, A. V. Vasilyev, V. G. Nenajdenko, *Tetrahedron Lett*. 2014, **55**, 6851-6855.

8. R.O. Iakovenko, V. M. Muzalevskiy, V. G. Nenajdenko, A. V. Vasilyev, *Russ. J. Org. Chem.* 2015, **51**, 436-438.

9. a) G. A. Olah, G. K. S. Prakash, A. Molnar, J. Sommer, Superacid Chemistry*;* Wiley: New York, 2009; b) G. A. Olah, D. A. Klumpp, Superelectrophiles and Their Chemistry*;* Wiley: New York, 2008; c) A. V. Vasilyev, *Russ. Chem. Rev.* 2013, **82**, 187-203.

10. a) R. G. Parr, L. V. Szentpaly, S. Liu, *J. Am. Chem. Soc.* 1999, **121**, 1922-1924; b) P. K. Chattaraj, S. Giri, S. Duley, *Chem. Rev.* 2011, **111**, PR43-PR75.

11. V. G. Nenajdenko, N. E. Shevchenko, E. S. Balenkova, I. V. Alabugin, *Chem. Rev.* 2003, **103**, 229–282.

12. a) T. Ohwada, N. Yamagata, K. Shudo, *J. Am. Chem. Soc.* 1991, **113**, 1364-1373; b) T. Suzuki, T. Ohwada, K. Shudo, *J. Am. Chem. Soc.* 1997, **119**, 6774-6780; c) K. Yu. Koltunov, S. Walspurger, J. Sommer, *Tetrahedron Lett*. 2005, **46**, 8391-8394; d) J. Guillon, P. Dallemange, J.-M. Leger, J. Sopkova, P. R. Bovy, C. Jarry, S. Rault, *Bioorg. Med. Chem.* 2002, **10**, 6851-1043-1050; e) G. K. S. Prakash, P. Yan, B. Torok, G. A. Olah, *Catalysis Lett*. 2003, **87**, 109-112; f) R. Rendy, Y. Zhang, A. Gomez, D. A. Klumpp, *J. Org. Chem.* 2004, **69**, 2340-2347; g) S. Chassaing, M. Kumarraja, P. Pale, J. Sommer, *Org. Lett.* 2007, **9**, 3889-3892; h) A. G. Posternak, R. Yu. Garlyuskayte, L. M. Yagupolskii, *J. Fluorine Chem.* 2010, **131**, 274-277; i) G. K. S. Prakash, F. Paknia, A. Narayanan, G. Rasul, T. Mathew, G. A. Olah, *J. Fluorine Chem.* 2012, **143**, 292–302; j) B. V. Ramulu, A. G. K. Reddy, G. Satyanarayana, *Synlett.* 2013, **24**, 868-872; k) W. Yin, Y. Ma, J. Xu, Y. Zhao, *J. Org. Chem.* 2006, **71**, 4312-4315; l) Y. Zhou, X. Li, S. Hou, J. Xu, *J. Mol. Cat. A : Chem.* 2012, **365**, 203-211; m) K. Yu. Koltunov, S. Walspurger, J. Sommer, *Chem. Comm*. 2004, 1754-1755; n) f) D. A. Klumpp, R. Rendy, Y. Zhang, A. Gomez, A. McElrea *Org. Lett.* 2004, **6**, 1789-1792; o) K. Yu. Koltunov, S. Walspurger, J. Sommer, *Tetrahedron Lett*. 2004, **45**, 3547-3549; p) D.N. Zakusilo, D.S. Ryabukhin, I. A. Boyarskaya, O. S. Yuzikhin, A. V. Vasilyev, *Tetrahedron*. 2015, **71**, 102-108; q) K.

Yu. Koltunov, S. Walspurger, J. Sommer, *Eur. J. Org. Chem*. 2004, 4039-4047; r) K. Yu. Koltunov, M. M. Shakirov, I. B. Repinskaya, V. A. Koptug, *Zh. Or. Khim. (in Russ.)*, 1991, **27**, 2622-2623; r) K. Yu. Koltunov, M. M. Shakirov, I. B. Repinskaya, V. A. Koptug, *Zh. Or. Khim. (in Russ.)*, 1991, **27**, 2622-2623; s) K. Yu. Koltunov, I. B. Repinskaya, *Zh. Or. Khim. (in Russ.)*, 1994, **30**, 90-93; t) A. V. Vasilyev, S. Walspurger, M. Haouas, J. Sommer, P. Pale, A. P. Rudenko, *Org. Biomol. Chem.* 2004, **2**, 3483-3489.

13. a) C. Aubert, J.-P. Bégué, D. Bonnet-Delpon, D. Mesureur, *J. Chem. Soc., Perkin Trans. 1* 1989, 395-399; b) A. Abouabdellah, C. Aubert, J.-P. Begue, D. Bonnet-Delpon, J. Guilhem, *J. Chem. Soc., Perkin Trans. 1* 1991, 1397-1403; c) K. Dong, Y. Li, Zh. Wang, K. Ding, *Angew. Chem. Int. Ed.* 2013, **52**, 14191-14195; d) R. J. Lorentzen, J. H. Brewster, H. E. Smith, *J. Am. Chem. Soc.* 1992, **114***, 2181-2187; e) K. Kundu, J. V. McCullagh, A. T. Morehead Jr., *J. Am. Chem. Soc.* 2005, **127**, 16042-16043; f) M. J. O'Connor, K. N. Boblak, M. J. Topinka, P. J. Kindelin, J. M. Briski, Ch. Zheng, D. A. Klumpp, *J. Am. Chem. Soc.* 2010, **132**, 3266–3267; g) P. G. Gassman, J. A. Ray, P. G. Wenthold, J. W. *J.* Mickelson, *Org. Chem.* 1991, **56**, 5143-5146; h) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro, N. Shibata, *Org. Lett.* 2011, **13**, 3972-3975.

14. E. L. Eliel, S. H. Wilen, L. N. Mander, Stereochemistry of Organic Compounds; Wiley: New York, 1994.

15. G. I. McGrew, J. Temaismithi, P. J. Carroll, P. J. Walsh, *Angew. Chem., Int. Ed.* 2010, **49**, 5541-554.

16. a) M. G. Gorbunova, I. I. Gerus, V. P. Kukhar, *J. Fluorine Chem.* 1993, **65**, 25-28; b) N. Matsumoto, M. Takahashi, *Tetrahedron Lett.* 2005, **46**, 5551-5554; c) S. V. Pazenok, I. I. Geus, E. A. Chaika, L. M. Yagupol'skiy, *Zh. Org. Khim.* 1989, **25**, 379-381.

17. A. C. Howlett, *Prostaglandins Other Lipid Mediat.* 2002, **68-69**, 619–631.

18. R. G. Pertwee, *Int. J. Obes.* 2006, **30**, S13-S18.

19. R. G. Pertwee, *Exp. Opin. Invest. Drugs* 2000, **9**, 1553–1571.

20. C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, *J. Pharmacol. Exp. Ther.* 1998, **284**, 291-297.

21. B. Dean, S. Sundram, R. Bradbury, E. Scarr, D. Copolov, *Neurosci.* 2001, **103**, 9-15.

22. V. Vichai, K. Kirtikara, *Nat. Protoc.* 2006, **1**, 1112-1116.

23. B. Bosier, G. G. Mucciouli, E. Hermans, D. M. Lambert, *Biochem. Pharmacol.* 2010, **80**, 1-12.

24. M. Pazos, E. Núñez, C. Benito, R. Tolón, J. Romero, *Pharmacol. Biochem. Behav.* 2005, **81**, 239–247.

25. Y. Cheng, S. A. Hitchcock, *Expert Opin. Investig. Drugs* 2007, **16**, 951–965.

26. C. Benito, E. Núñez, R. M. Tolón, E. J. Carrier, A. Rábano, C. J. Hillard, J. Romero, *J. Neurosci.* 2003, **23**, 11136–11141.

27. *SHELXS*; Sheldrick, G. M. *Acta Cryst.* 2008, **A64**, 112-122.

28. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.* 2009, **42**, 339-341.

29. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *GAUSSIAN 03, Revision B.01*; Gaussian, Inc., Pittsburgh, PA, 2003.