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Reactions of CF$_3$-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

CF$_3$-enones, Brønsted superacids, trifluoromethyl group, indanes, endocannabinoid system, cannabinoid receptor ligands
Abstract

4-Aryl-1,1,1-trifluorobut-3-en-2-ones ArCH=CHCOCF₃ (CF₃-enones) react with arenes in excess of Brønsted superacids (TfOH, FSO₃H) to give, stereoselectively, trans-1,3-diaryl-1-trifluoromethyl indanes in 35-85% yields. The reaction intermediates, the O-protonated ArCH=CHC(OH⁺)CF₃ and the O,C-diprotonated ArHC⁺CH₂C(OH⁺)CF₃ species, have been studied by means of ¹H, ¹³C, ¹⁹F 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 CF₃-indanes is a result of cascade reaction of protonated CF₃-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 CB₁ and CB₂ types. The most potent compound showed sub-micromolar affinity for both receptor subtypes with a 6-fold selectivity toward CB₂ receptor with no appreciable cytotoxicity toward SHSY5Y cells.

Graphical Abstract

Introduction

1,1,1-Trifluorobut-3-en-2-ones (CF₃-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 CF₃-enones have been developed. The combination of a conjugated carbon-carbon double bond and a CF₃CO-group present in these compounds, results in
their unique electrophilic properties, leading to the reactions at either the carbonyl group\textsuperscript{3} or the double bond\textsuperscript{3} - or at both of these structural fragments.\textsuperscript{4} CF\textsubscript{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.\textsuperscript{5}

In continuation of our previous studies of reactions of CF\textsubscript{3}-alkynes in Brønsted superacids,\textsuperscript{6} and CF\textsubscript{3}-allyl alcohols under action of Lewis acids,\textsuperscript{7} we became interested in studying of the fate of CF\textsubscript{3}-enones 1a-h (Figure 1) under similar superelectrophilic activation. In preliminary short communication\textsuperscript{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\textsubscript{3}H)\textsuperscript{9} to significant enhancement of electrophilic properties of CF\textsubscript{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.

![Figure 1. Starting CF\textsubscript{3}-enones 1a-h used in this study](image)

**Results and discussion**

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

Protonation of conjugated enones\textsuperscript{9a,b} or ynones\textsuperscript{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\textsubscript{3}-enones system of compounds 1 gives consequently cations A and dications B (Scheme 1). The latter species are considered as superelectrophiles.\textsuperscript{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.

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 $\omega$ 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.
Thus, the DFT calculations predict that in principle both cationic species A and B derived from 1 (Scheme 1) may act as electrophiles. Atom C² is the reactive center in dications B. Cations A may possess two centers (atoms C² and C⁴) for the reaction with nucleophiles.

NMR study of CF₃-enones protonation in superacids

In order to confirm DFT predictions we investigated protonation of CF₃-enones in TfOH and FSO₃H at various temperatures by means of NMR. It was found, that CF₃-enones 1a,c,d,f,h afforded stable O-protonated species A₁, A₃, A₄, A₆, A₇, respectively, at temperatures below -20 °C. ¹H, ¹³C, and ¹⁹F NMR data of these carbocations and the corresponding starting materials are given in SI (Table S1). ¹³C 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 CF₃-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 H4 and carbon C4 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 C4 and contribution of the corresponding resonance structure \( \text{A'} \) (Table S1). On the other hand, the carbonyl carbon C2 (in \(^{13}\)C NMR) underwent only slight upfield shifts upon protonation. That additionally argues in favor of form \( \text{A'} \). 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 \( \text{A''} \) (Table S1), in which restricted rotation around bond C4–C1 is possible. This resonance form has a significant contribution in case of para-methoxy substituted cation \( \text{A''6} \), in which the signal of Cp 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 \( \text{A''7} \) (Table S1).

Thus, NMR data indicates a significant delocalization of positive charge from C2 to C4 in the O-protonated species A, despite the fact that the DFT calculations did not predict a substantial charge redistribution (see Table S9). These data suggest that carbocations A are likely to react with nucleophiles primarily at C4.

Reactivity of CF3-enones with arenes in superacids

Having gathered the NMR data relevant to the protonation of CF3-enones 1, we proceeded to study the behavior of compounds 1 in superacids. In TfOH at 20 °C, CF3-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 CF₃-enone 1a with benzene (12 equiv.) under the action of various acids

![Chemical structure of 1a and 2a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Reaction products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acid</td>
<td>T, °C</td>
</tr>
<tr>
<td>1</td>
<td>TfOH (50 equiv.)</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>TfOH (5 equiv.), CH₂Cl₂(co-solvent)</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>TfOH (1 equiv.), CH₂Cl₂(co-solvent)</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>H₂SO₄ (750 equiv.)</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>FSO₃H (80 equiv.), SO₂(co-solvent)</td>
<td>-40</td>
</tr>
<tr>
<td>6</td>
<td>FSO₃H (80 equiv.)</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>TfOH (50 equiv.)</td>
<td>-20</td>
</tr>
<tr>
<td>8</td>
<td>AlBr₃ (5 equiv.)</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>AlBr₃ (5 equiv.), CH₂Cl₂(co-solvent)</td>
<td>-40</td>
</tr>
<tr>
<td>10</td>
<td>AlCl₃ (5 equiv.), CH₂Cl₂(co-solvent)</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>FeCl₃ (5 equiv.)</td>
<td>20</td>
</tr>
</tbody>
</table>

Notes. *Complete conversion of initial 1a. *Incomplete conversion (~30%) of initial 1a. †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, FSO3H or TfOH), CF3-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 Bronsted (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 C2 and C4 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 acids12d-j and their chloro anhydrides12k-l or amides,m-nq 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 CF3-substituent to enone system of 1a leads to additional electrophilic activation of carbonyl carbon C2, which takes part in reaction with benzene (Table 1). It should be also noted that for some enones12f–q 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 1H, 13C, 19F 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

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-Trifluoromethylated 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.\textsuperscript{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)$^\circ$ for 2g to 32.0(1)$^\circ$ for 2c. CF$_3$-group deviates to the envelope lid (the angle of deviation change weakly from 110.6 (1)$^\circ$ for 2h to 111.9(1)$^\circ$ for 2g). The benzene ring plane of the indane system has no deviation from envelope base plate practically (limits are from 0.3(1)$^\circ$ for 2b to 3.1(1)$^\circ$ for 2g). Planes of aryl substituents are bended to envelope base with angle 72.33(6)$^\circ$ for 2g ÷ 77.1(1)$^\circ$ for 2a and 66.74(9)$^\circ$ for 2h ÷ 76.90(6)$^\circ$ 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\textsuperscript{1} and C\textsuperscript{3} of indane system changes very slightly the configuration of indane core.\textsuperscript{13f,15}

The formation of indanes 2 indicates that both electrophilic carbons C\textsuperscript{2} and C\textsuperscript{4} of cationic intermediates A or B participated in the reaction. Interestingly, electron-rich substrates, such as o-xylene or thiophene, reacted with CF\textsubscript{3}-enones 1a,c in FSO\textsubscript{3}H at -80...-60 °C, i.e. under the conditions that favor the formation of O-protonated species A\textsubscript{1}, A\textsubscript{3} (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\textsubscript{3}H) gave only the corresponding 3,3-diarylbutanone 3a in 77 % yield (Scheme 3). The reaction of CF\textsubscript{3}-enone 1e with benzene in FSO\textsubscript{3}H at -60 °C gave CF\textsubscript{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 CF3-enones 1](image)

All these data clearly demonstrate that cations A are generally able to react at C\textsuperscript{4} with electron rich arenes and heteroarenes. However, the highly electrophilic versions of these cations, like A\textsubscript{5} (based on its $\omega$ values presented in Table S9) generated from 1e, can also react with less nucleophilic
arenes like benzene, also at C\textsuperscript{4} (Scheme 3). Finally, we believe that the reactions of CF\textsubscript{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\textsuperscript{4} and C\textsuperscript{2} respectively. Based on this conclusion, one can propose the following reaction pathways for the transformation of CF\textsubscript{3}-enones 1 into indanes 2 (Scheme 4). The reaction of arenes with cation A at carbon C\textsuperscript{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\textsuperscript{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 CF₃-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](image)

**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 C1 of indane system (Scheme 4). Geometry of this species exhibits that cone angle with the apex at atom C3 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\textsuperscript{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.$^{12f, q-1}$

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 buthoxypnene 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](image)

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.
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 \(\Delta^9\)-tetrahydrocannabinol (\(\Delta^9\)-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 – \textit{vide infra}) further supported our hypothesis of investigating the potential binding affinity of these molecules toward cannabinoid receptors.

\[\text{Figure 5. Endogenous (AEA and 2-AG) and natural (\(\Delta^9\)-THC) and synthetic (SR141716A, JWH015 and LY320135) cannabinoid receptor ligands}\]

Eight compounds \(2a, 2c, 2d-h,l\) were screened for their ability to displace \([^3H]\text{CP55,940}\) (the radiolabelled analogue of CP55,940, a potent, non-selective classical CB\(_1\) and CB\(_2\) ligand\(^{21}\)) from CB\(_1\)
and CB₂ 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](image.png)

**Figure 6** (a) Binding properties of compound 2a, 2c, 2d-h,l tested at the concentration of 1 µM to CB₁ and CB₂ 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, 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 CB₂ receptor and a 6-fold selectivity vs. CB₁ 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 CB1/CB2 ligands, especially with LY320135, suggesting potentially similar functional signaling by our trans-diaryl indanes (Figure 8).\textsuperscript{23}

<table>
<thead>
<tr>
<th>Ki value (mean and 95%, CI) µM</th>
<th>hCB\textsubscript{1}</th>
<th>hCB\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>1.35 (0.91-2.05)</td>
<td>0.55 (0.42-0.73)</td>
</tr>
<tr>
<td>2e</td>
<td>6.55 (4.92-8.71)</td>
<td>1.19 (0.75-1.68)</td>
</tr>
<tr>
<td>2h</td>
<td>0.75 (0.48-1.15)</td>
<td>0.12 (0.07-0.20)</td>
</tr>
</tbody>
</table>

**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. 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 CB₂ receptors which are a highly promising pharmacological target for treating inflammatory and neuropathic pain and neurodegenerative diseases.

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 ¹H, ¹³C, ¹⁹F 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 $^1$H, $^{19}$F and $^{13}$C NMR spectra respectively) or Bruker DPX 300 (at 300 and 75 MHz for $^1$H and $^{13}$C NMR spectra respectively) spectrometers at 25 °C. The residual proton-solvent peak CDCl$_3$ (δ 7.26 ppm) for $^1$H 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$_3$H were performed on Bruker AVANCE III spectrometer (at 500, 476 and 125 MHz for $^1$H, $^{19}$F and $^{13}$C NMR spectra respectively). NMR spectra in superacids were referenced to the signal of CH$_2$Cl$_2$ added as internal standard: δ 5.32 ppm for $^1$H 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 MoKα radiation (2a, 2b) and Agilent Technologies SuperNova using monochromated CuKα (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\textsuperscript{27} incorporated in the OLEX2 program package.\textsuperscript{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 1.5$U_{eq}$(C) and C–H 0.96 Å for the CH$_3$ groups, $U_{iso}(H)$ set to 1.2$U_{eq}$(C) and C–H 0.97 Å for the CH$_2$ groups, $U_{iso}(H)$ set to 1.2$U_{eq}$(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\textsuperscript{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.\textsuperscript{1b,f-h}

**General procedure for reaction of compounds 1a-g with arenes in superacids CF$_3$SO$_3$H or FSO$_3$H. 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$_3$H (at -80…-60 °C) (1 mL, co-solvents SO$_2$ or CH$_2$Cl$_2$) 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$_2$SO$_4$. 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 \( \text{FSO}_3 \text{H} \) 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.

\( \text{(1RS,3RS)-1-Trifluoromethyl-1,3-diphenylindane (2a).} \) Yield 65 mg, 84%. Colorless solid, mp 106-108°C (MeOH). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \), 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) \( \delta \), ppm: 46.9 (CH), 48.3 (CH\(_2\)), 60.8 (q, CFCF\(_3\), \( J = 26.4 \) 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) \( \delta \), ppm: -69.16 (s, CF\(_3\)). MS (GC-MS, EI), m/z, (\( \text{I}_{\text{rel.}}, \% \)) – 338 \( \text{M}^+ \) (3), 260 (100), 191 (50). HRMS: C\(_{22}\)H\(_{17}\)F\(_3\) found 338.1285 \( \text{M}^+ \); calcd. 338.1282.

\( \text{(1SR,3RS)-1-Trifluoromethyl-1,3-diphenylindane (cis-2a).} \) Obtained as 1:1 mixture with indane 2a. Yield 25 mg, 80%. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \), 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) \( \delta \), ppm: 48.1 (CH\(_2\)), 49.9 (CH), 61.7 (q, CFCF\(_3\), \( J = 25.3 \) 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) \( \delta \), ppm: -69.36 (s, CF\(_3\)). MS (GC-MS, EI), m/z, (\( \text{I}_{\text{rel.}}, \% \)) – 338 \( \text{M}^+ \) (100), 269 (100), 260 (90), 191 (100). HRMS: C\(_{22}\)H\(_{17}\)F\(_3\) found 338.1285 \( \text{M}^+ \); calcd. 338.1282.

\( \text{(1RS,3RS)-1-Trifluoromethyl-5,6-dimethyl-1-(3,4-dimethylphenyl)-3-phenylindane (2b).} \) Yield 80 mg, 77%. Colorless solid, mp 106-108°C (MeOH). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \), 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). $^1$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$_3$O$_4$ 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$_3$, 376 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)-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 Hz), 2.93 (dd, 1H, 12.5 Hz, 7 Hz), 3.76 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 4.05 (dd, 1H, $J = 7$ Hz, 11 Hz), 6.41 (s, 1H), 6.71-6.78 (m, 2H), 6.88 (s, 1H), 7.03 (s, 1H), 7.22 (d, 2H, $J = 7$ Hz), 7.22-7.25 (m, 1H), 7.31 (t, 2H, $J = 7.4$ Hz). $^{13}$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.
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) \(\delta\), ppm: 46.9 (q, CH\(_2\)), 47.7 (CH), 60.8 (q, 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) \(\delta\), 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) \(\delta\), 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) \(\delta\), 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, CF\(_3\), \(J = 26.2\) Hz), 124.3, 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) \(\delta\), 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) \(\delta\), 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) \(\delta\), 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, 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) \(\delta\),
ppm: -68.72 (s, CF₃). MS (GC-MS, EI), m/z, (Iᵣₑˡ, %) – 428 [M⁺] (30), 359 (15), 322 (100), 253 (20). HRMS: C₂₆H₂₄F₃Cl found 428.1517 M⁺; calcd. 428.1519.

(1RS,3RS)-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). ¹H NMR (CDCl₃, 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, OCH₃), 3.80 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 4.05 (dd, 1H, J = 10.6 Hz, 6.8 Hz), 6.38 (s, 1H), 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). ¹³C NMR (CDCl₃, 100 MHz) δ, ppm: 47.7 (CH), 48.0 (CH₂), 55.97 (OMe), 55.99 (OMe), 56.12 (OMe), 60.4 (q, C-F, J = 26.3 Hz), 107.8, 108.3 (d, J = 0.8 Hz), 110.7, 111.8, 121.1, 127.7 (q, CF₃, 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. ¹⁹F NMR (CDCl₃, 376 MHz) δ, ppm: -69.25 (s, CF₃). MS (GC-MS, EI), m/z, (Iᵣₑˡ, %) – 492 [M⁺] (50), 423 (40), 354 (100). HRMS: C₂₆H₂₄F₃O₄Cl found 492.1318 M⁺; calcd. 492.1315.

(1RS,3RS)-1-Trifluoromethyl-5-methoxy-1,3-diphenylindane (2i). Yield 11 mg, 76%. Colorless solid, mp 102-104°C (MeOH). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 100 MHz) δ, ppm: 47.3 (CH₂), 48.4 (CH), 55.6 (OMe), 60.2 (q, C-F, J = 29.5 Hz), 110.6, 113.5, 126.6 (q, CHCCF₃, J = 1 Hz), 127.2, 127.7 (q, CF₃, 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. ¹⁹F NMR (CDCl₃, 376 MHz) δ, ppm: -69.46 (s, CF₃). MS (GC-MS, EI), m/z, (Iᵣₑˡ, %) – 368 M⁺ (80), 299 (100), 290 (25), 221 (30). HRMS: C₂₃H₁₉F₃O 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. ¹H NMR (CDCl₃, 400 MHz) δ, ppm: 2.32 (s, 3H, OMe), 3.40-3.52 (m, 2H, AB-system, CH₂), 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). ¹³C NMR (CDCl₃, 100 MHz) δ, ppm: 21.2 (CH₃), 40.0 (CH), 44.0 (CH₂), 115.5 (CF₃, J
\( \text{= 292 Hz), 124.40, 124.27, 126.9, 127.4, 129.7, 137.2, 139.3, 146.9, 189.0 (q, COCF}_3, J = 35.7 \text{ Hz).} \)

\(^{19}\text{F NMR (CDCl}_3, 376 \text{ MHz) } \delta, \text{ ppm: -79.39 (s, CF}_3\text{). MS (GC-MS, EI), m/z, (I}_{\text{rel.}}, \% - 298 M^+ (20), 283 \text{ [M-CH}_3]^+ (15), 229 \text{ [M-CF}_3]^+ (7), 187 \text{ [M-CH}_2\text{COCF}_3]^+ (100). HRMS: C}_{14}\text{H}_{13}\text{F}_3\text{OS found 286.0640 } M^+; \text{ calcd. 286.0640.} \)

\text{1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-phenylbutan-2-one (3b). Yield 44 mg, 68%. Colorless oil.} \(^1\text{H NMR (CDCl}_3, 400 \text{ MHz) } \delta, \text{ ppm: 3.48 (d, 2H, CH}_2, J = 7.5 \text{ Hz), 3.77 (s, 3H, OMe), 4.63 (t, 1H, CH, J = 7.5 \text{ Hz), 6.73-6.77 (m, 2H), 6.82 (d, 1H, J = 7.8 \text{ Hz), 7.20-7.25 (m, 4H), 7.28-7.34 (m, 2H).} \)} \]^1\text{C NMR (CDCl}_3, 100 \text{ MHz) } \delta, \text{ ppm: 42.6 (CH}_2\text{), 44.7, 55.3, 109.8, 112.0, 115.6 (CF}_3, J = 292 \text{ Hz), 117.5, 127.1, 127.6, 129.0, 130.0, 142.4, 144.2, 160.0, 189.4 (q, COCF}_3, J = 35.5 \text{ Hz).} \)^{19}\text{F NMR (CDCl}_3, 376 \text{ MHz) } \delta, \text{ ppm: -79.38 (s, CF}_3\text{). MS (GC-MS, EI), m/z, (I}_{\text{rel.}}, \% - 308 M^+ (100), 239 (23), 197 (95). HRMS: C}_{17}\text{H}_{15}\text{F}_2\text{O}_2 \text{ found 308.1021 } M^+; \text{ calcd. 308.1024.} \)

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


