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PAPER

Synthesis and antidepressant-like activity of selenophenes obtained *via* iron(III)–PhSeSePh-mediated cyclization of *Z*-selenoenynes†

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We present here the synthesis and antidepressant-like action of a series of 2,5-disubstituted-3-(organoseleno)-selenophenes prepared by a novel synthetic route, the $FeCl_3$–diorganyl dichalcogenide-mediated intramolecular cyclization of (*Z*)-chalcogenoenynes. The cyclized products were obtained in good yields. The results showed that **2c**, **2d**, **2e** and **2o**, evaluated in the mouse forced-swimming test, elicited an antidepressant-like activity. The studies clearly show that the phenyl group at the 2-position and an organoselenium group at the 3-position of the selenophene ring are essential for the antidepressant-like activity of selenophenes. A close inspection of the results also revealed that the fluorophenyl portion in the organoselenium group is fundamental for the antidepressant-like action of this class of organochalcogens.

Introduction

Depression is a common, debilitating, life-threatening illness with a significant incidence in the population. Numerous antidepressant drugs are now available, presumably acting *via* different mechanisms. The most widely used treatment for depression is based on drugs affecting serotonin (5-HT) neurotransmission, such as those inhibiting 5-HT reuptake at nerve terminals (*e.g.*, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline).[1] Selective serotonin reuptake inhibitors (SSRIs) show antidepressant action in both clinical and experimental studies.[2] However, the heterogeneity of the clinical responses to antidepressants and susceptibility to adverse effects are the major clinical problems. In this sense, new directions for antidepressant treatment have been developed. Recently, we reported that 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene produces an antidepressant-like action in experimental models predictive of depression and this effect is mediated through an interaction with the serotonergic system.[3] In this way, interest in the chemistry of selenophenes has increased remarkably due to their chemical properties,[4] biological activity and pharmaceutical potential.[3,5] Some selenophene compounds are known as effective anti-bacterial,[6] anti-apoptotic[7] and anti-tumoral[8] agents. Previous reports from our research group have shown the hepatoprotective,[9] anticonvulsant, antioxidant,[10] antinociceptive and anti-allodynic[11] properties of 3-alkynyl selenophene. Chalcogenophene heterocycles and their derivatives have also numerous uses in the fields of physical organic chemistry, materials chemistry and organic synthesis. In fact, chalcogenophene oligomers are compounds of current interest because many of them show biological, optical and electrochemical activities.[12] A great number of these heterocycles have been synthesized and their chemistry has attracted a good deal of interest and activity from a variety of standpoints such as structures, stereochemistry, reactivities and applications to organic synthesis.[13] Regarding the synthesis of the heterocycles, the transition-metal catalyzed cyclization reaction of simple acyclic precursors is one of the most attractive ways to directly construct complicated molecules under mild conditions.[14] In this way, palladium is one of the most common transition metals used,[15] although it sometimes displays intolerance to some functionalities or proceeds with a lack of regioselectivity. Recently, we presented our contribution to this field by developing a general and mild protocol for seleno- and tellurophene synthesis *via* the reaction of enynes with diorganoyl dichalcogenides, catalyzed by CuI; however, the use of alkyl enyne substrates was a limiting factor of this methodology.[13a,16] During the past years, there has been an impressive increasing attention to the development of environmentally benign protocols and the great challenge for chemists is to apply cost-effective, green, mild and alternative methodologies.[17] In this sense, iron salts have appeared as a versatile alternative, due to their low price, low toxicity and environmentally benign properties. Considering these aspects, many findings concerning iron-mediated organic transformations have been reported. For example, iron trichloride was applied in the cross-coupling of Grignard reagents with several organic electrophiles,[18] iron-catalyzed C–N,[19] C–O,[20] and C–S[21] bond formation. Among these transformations iron salts have also emerged as alternative and promising catalysts or promoters for the cyclization process.[22]

In continuation of our studies on the preparation of novel heterocyclic systems containing selenium, and based on the fact

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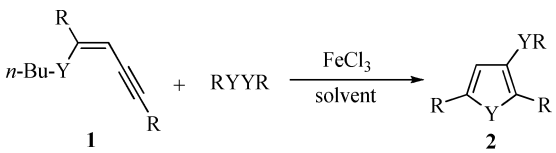
that selenophenes have antidepressant-like activity, we synthesized new 2,5-disubstituted-3-(organoseleno)-selenophenes to investigate the structure–antidepressant activity relationship. Thus, our findings on $FeCl_3$/RSeSeR,[23] as an alternative system to IPy_2BF_4,[24] halogen[25] NXS,[26] trichloroisocyanuric acid (TCCA),[27] $I(coll)_2PF_6/BF_3{\cdot}3OEt_2$,[28] organoselenium[29] and organotellurium electrophiles[30] to promote cyclization of functionalized alkynes, associated with the fact that currently there are no reports concerning the cyclization of enynes using a $FeCl_3$/RSeSeR system to prepare selenophene derivatives, encouraged us to examine if 3-organoseleno chalcogenophenes **2** would be generated from (*Z*)-chalcogenoenynes **1** *via* intramolecular cyclization reactions using $FeCl_3$/RSeSeR as the cyclizing agent (Scheme 1).

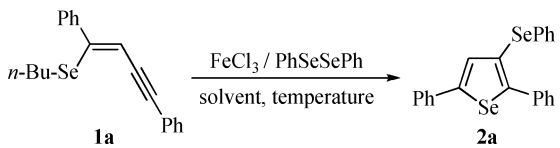


Scheme 1 General scheme.

Chemistry

The starting (*Z*)-chalcogenoenynes **1** were readily available by using the process of hydrochalcogenation of alkynes.[31] Our initial studies on the cyclization focused on the development of an optimum set of reaction conditions. We investigated the procedure with respect to five key variables: (1) solvents, (2) diorganyl diselenide loading, (3) iron trichloride loading, (4) temperature and (5) atmosphere. In this way, the optimization process was performed using selenoenyne **1a** and diphenyl diselenide as standard substrates. Thus, a mixture of diphenyl diselenide (0.25 mmol) and $FeCl_3$ (0.25 mmol), using CH_3CN as solvent, was reacted with **1a** (0.25 mmol) under reflux for 4 h. As shown in Table 1, using these reaction conditions, the desired product **2a** was obtained in 77% yield (Table 1, entry 1). Regarding the temperature, the use of a lower temperature (25 °C) proved to be worse than the use of reflux (Table 1, entry 2). To identify the solvent potentially suitable for the cyclization, we initially chose CH_3CN, MeOH, DMSO and THF. All solvents tested gave the desired product **2a** in acceptable yields (Table 1, entries 1–12). However, we chose CH_2Cl_2 as solvent because it gave the product not only in a similar yield but also in a shorter reaction time (Table 1, entry 11). Next, the amount of $FeCl_3$ was investigated by varying from a catalytic ratio (0.1 equiv) to 1.5 equiv, with the best result obtained

Table 1 Influence of reaction conditions in the $FeCl_3$/PhSeSePh cyclization of (*Z*)-selenoenyne **1a**[a]



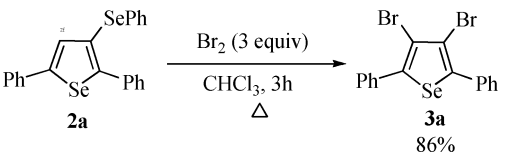
Entry	[Fe] (equiv)	Solvent	PhSeSePh (equiv)	Atmosphere	Time (h)	Yield (%)
1	$FeCl_3$ (1)	CH_3CN	1.0	argon	4	77
2[b]	$FeCl_3$ (1)	CH_3CN	1.0	argon	6	67
3	$FeCl_3$ (1)	CH_3CN	2.0	argon	3	68
4	$FeCl_3$ (1)	CH_3CN	—	argon	12	—[c]
5	$FeCl_3$ (0.1)	CH_3CN	1.0	argon	24	26
6	$FeCl_3$ (1)	MeOH	1.0	argon	24	80
7	$FeCl_3$ (1)	MeOH	0.55	argon	24	68
8	$FeCl_3$ (1.5)	MeOH	0.55	argon	24	70
9	$FeCl_3$ (1)	DMSO	1.0	argon	36	54
10	$FeCl_3$ (1)	THF	1.0	argon	24	69
11	$FeCl_3$ (1)	CH_2Cl_2	1.0	argon	2	74
12	$FeCl_3$ (1)	CH_2Cl_2	0.55	argon	3	74
13	$FeCl_3{\cdot}6H_2O$ (1)	CH_2Cl_2	0.55	argon	24	68
14	$Fe(acac)_3$ (1)	CH_2Cl_2	0.55	argon	24	—[c]
15	$FeCl_2{\cdot}4H_2O$ (1)	CH_2Cl_2	0.55	argon	24	Trace
16	$K_3Fe(CN)_6$ (1)	CH_2Cl_2	0.55	argon	24	—[c]
17	$FeCl_3$ (0.1)	DMSO	1.0	argon	24	20
18	$FeCl_3$ (0.1)	DMSO	1.0	air atmosphere	24	55
19	$FeCl_3$ (0.1)	DMSO	2.0	air atmosphere	24	50
20	$FeCl_3$ (0.1)	DMSO	0.55	air atmosphere	24	50
21	$FeCl_3$ (0.1)	DMSO	0.55	oxygen atmosphere	24	43
22	$FeCl_3$ (0.1)	CH_3CN	0.55	air atmosphere	36	23
23	$FeCl_3$ (0.1)	CH_3NO_2	0.55	air atmosphere	24	20
24	$FeCl_3$ (0.1)	DMF	0.55	air atmosphere	24	15
25	$FeCl_3$ (0.1)	Dioxane	0.55	air atmosphere	24	25
26	$FeCl_3$ (0.1)	CH_2Cl_2	0.55	air atmosphere	24	20
27	$FeCl_3$ (0.1)	Toluene	0.55	air atmosphere	24	32
28	$FeCl_3$ (0.2)	DMSO	0.55	air atmosphere	12	67

[a] Reaction performed at 0.25 mmol scale in solvent (3 mL) and yields of **2** are given for isolated products. [b] Reaction carried out at room temperature. [c] (*Z*)-selenoenyne **1a** was recovered.

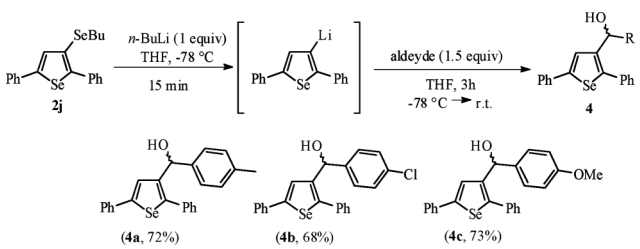
using 1.0 equiv (Table 1, entry 11). To better understand if the activity of the iron system is due to the different ligand partner type in the iron complex or to the effect of dry iron salt, some experiments were also carried out using $FeCl_3 \cdot 6H_2O$, $Fe(acac)_3$, $FeCl_3 \cdot 4H_2O$ and $K_3Fe(CN)_6$ and a very sluggish reactivity was observed (Table 1, entries 13–16). We observed that the amount of PhSeSePh affected the reaction result. Fortunately, decreasing the amount of PhSeSePh from 1.0 to 0.55 equiv did not modify the reaction behavior and the product was obtained in a similar yield (Table 1, entry 12). This result is significant because it suggests that the two portions of diphenyl diselenide (PhSe) were incorporated in the final product and indicates an atom economy, which is an important concept of green chemistry philosophy. Considering that the absence of air in the system could hamper the catalyst reactivity of iron reoxidation, we next hypothesized that the cyclization could be achieved under catalytic conditions, if one changes the inert reaction to an open atmosphere. A comparison of reaction run using rigorously dried systems (Table 1, entry 5) *versus* those run in an open atmosphere (Table 1, entry 18) showed that the yield was higher in the latter case. However, no significant improvement in the yield was found when an oxygen atmosphere was adopted (Table 1, entry 21). On the basis of this encouraging result, a range of other solvents was screened to find the best conditions that might be applied to the cyclization reaction using a catalytic system (Table 1, entries 19–29). We were pleased to observe that $FeCl_3$ (20 mol%) in DMSO efficiently catalyzed the cyclization of **1a** in an excellent isolated yield (Table 1, entry 28). This result is significant in order to make our methodology more attractive from an economic standpoint and eco-friendly. The above results suggest that while $FeCl_3$ (1 equiv), PhSeSePh (0.55 equiv) in CH_2Cl_2 at 40 °C were the best conditions to carry out the reaction under argon atmosphere, the use of PhSeSePh (0.55 equiv) in DMSO at 110 °C were the best conditions for the catalytic system ($FeCl_3$ 20 mol%) in an open atmosphere. After obtaining two sets of conditions (catalytic and non-catalytic) for the cyclization of **1a**, we next investigated the cyclization of several enynes with different diorganyl dichalcogenides (Table 2).

With the optimized conditions defined, we started the investigation of the scope of the cyclization process. Initially, we kept the enyne structures constant and studied the influence of different diorganyl dichalcogenides. No significant differences in yields were found with neutral, electron rich and electron poor diorganyl dichalcogenides (Table 2, entries 1–5). However, the cyclization using diorganyl dichalcogenides bearing a sterically hindered functionality gave only moderated yields (63 and 59%) under identical conditions (Table 2, entries 6 and 7). These results revealed that the reaction does not significantly depend on the electronic effects of the substituents in the aromatic ring of the diorganyl dichalcogenides but that it seems to be sensitive to the steric effects. Under the same conditions, diaryl ditellurides reacted similarly and products **2h–i** were obtained in moderate yields (Table 2, entries 8 and 9). Interestingly, the cyclization reaction of **1a** also proceeded smoothly with dialkyl diselenides and ditellurides but noticeably lower yields were obtained compared to the use of aryl derivatives. The yields obtained in the cyclization reaction using diselenides are consistently higher than those obtained with tellurides, partly because selenides are less susceptible to selenoxide elimination than the corresponding tellurides.[32] Other enynes having functionalities such as sterically hindered **1e**, electron poor aromatic rings **1f** and unsymmetrical system **1g** reacted without difficulty and gave excellent yields (Table 2, entries 12–15). Encouraged by the success of the cyclization reactions of aryl enynes with diorganyl dichalcogenides, we then turned our interests to the reactions of alkyl enynes. In accordance with previous observations made by us, selenoenyne cyclization *via* copper salts with (*Z*)-alkyl selenoenynes was markedly met with failure.[13a] Thankfully, the results summarized in Table 2 show that the optimized conditions described above proved to be general for the cyclization of alkyl selenoenynes with a large variety of functionalized diorganyl dichalcogenides. We were pleased to find out that all reactions afforded the desired selenophene products in good yields and substituents having either electron-donating or electron-withdrawing groups on the aromatic ring of diorganyl dichalcogenides have almost no significant effect on these reactions (Table 2, entries 16–24). Furthermore, both aryl and alkyl telluroenynes were successfully used as substrates affording the desired tellurophenes; even though, as expected, the yields of the cyclizations of alkyl telluroenynes were lower than those of aryl telluroenynes (Table 2, entries 25–28). The efficiency of this system was further extended to the cyclization reactions of various selenoenynes using the catalytic conditions determined in Table 1, entry 28. The obtained yields were good but considerably lower compared to the non-catalytic conditions (Table 2, entries 1–11; yields in parentheses).

In order to complete our investigation and to further prove the potential of 3-chalcogen selenophene derivatives as precursors for increasing molecular complexity, we tested the reactivity of these compounds toward halogenation and Li/Se exchange reactions. In this way, the reaction of **2a** with an excess of bromine in refluxing $CHCl_3$, afforded the resultant product **3a**, in 86% isolated yield (Scheme 2). This result is significant since these halogenated selenophenes find applications in transition metal-catalyzed cross-coupling reactions with various nucleophilic compounds for the preparation of more complex molecules of selenophenes.[33] In addition, the reaction of selenophene **2j** with *n*-butyllithium (1.0 equiv), THF (3 mL), at −78 °C gave the lithiated species. The lithiated species was trapped by aldehydes (1.5 equiv) at −78 °C and the reaction mixture was allowed to warm to room temperature, affording the secondary alcohols **4a–c** in good yields (Scheme 3).

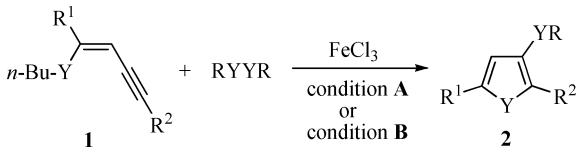


Scheme 2 Synthesis of 3,4-dibromoselenophene **3a**.



Scheme 3 Reactions of intermediate 3-lithio selenophene with aldehydes.

Table 2 Synthesis of 3-organochalcogen chalcogenophene derivatives **2**



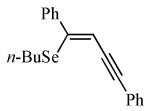
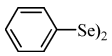
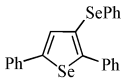
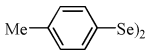
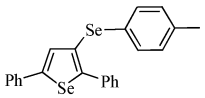
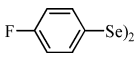
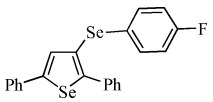
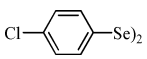
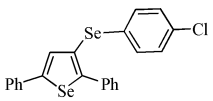
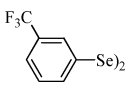
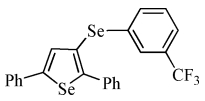
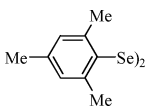
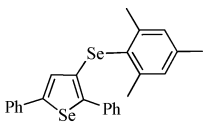
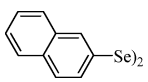
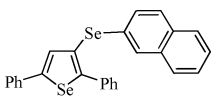
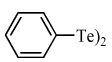
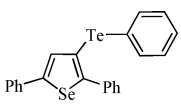
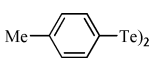
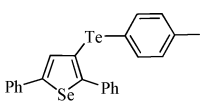
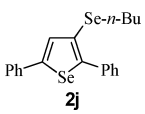
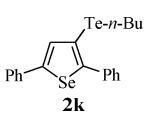
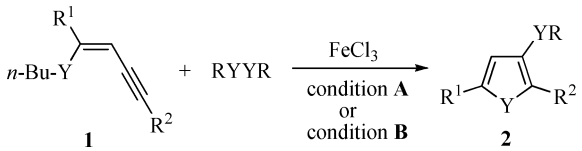
Entry	(*Z*)-enyne	RYYR	Product	Yield A% (B%)[a,b]
1	 **1a**		 **2a**	74 (67)
2	**1a**		 **2b**	81 (71)
3	**1a**		 **2c**	78 (73)
4	**1a**		 **2d**	79 (55)
5	**1a**		 **2e**	66 (57)
6	**1a**		 **2f**	63 (50)
7	**1a**		 **2g**	(59)
8	**1a**		 **2h**	36 (23)
9	**1a**		 **2i**	43
10	**1a**	*n*-BuSe)$_2$	 **2j**	60 (77)
11	**1a**	*n*-BuTe)$_2$	 **2k**	40 (30)

Table 2 (*Contd.*)



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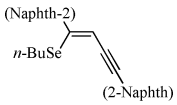
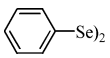
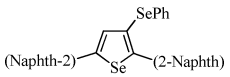
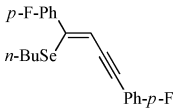
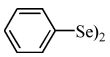
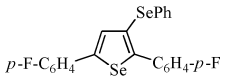
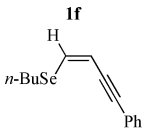
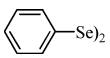
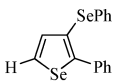
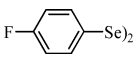
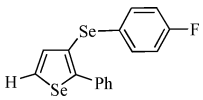
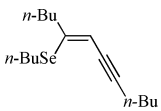
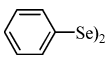
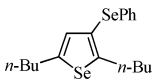
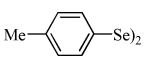
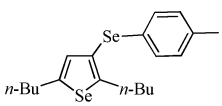
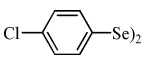
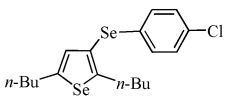
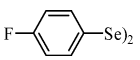
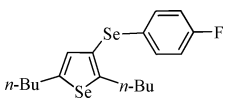
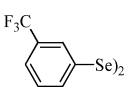
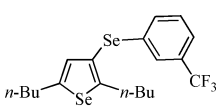
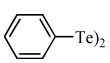
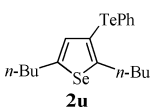
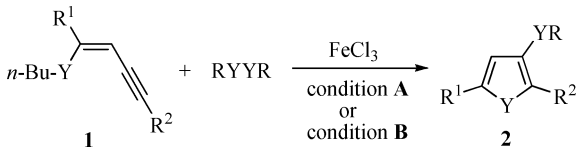
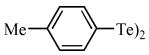
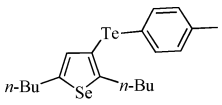
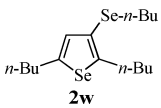
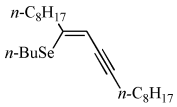
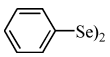
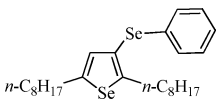
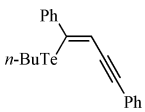
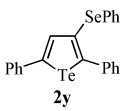
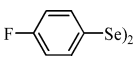
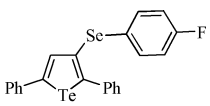
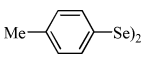
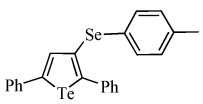
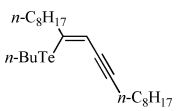
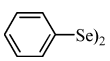
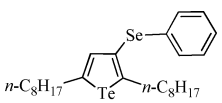
12	 **1e**		 **2l**	82
13	 **1f**		 **2m**	78
14	**1f**  **1g**		 **2n**	73
15	**1g**		 **2o**	66
16	 **1h**		 **2p**	67 (NR)
17	**1h**		 **2q**	58
18	**1h**		 **2r**	62
19	**1h**		 **2s**	54
20	**1h**		 **2t**	53
21	**1h**		 **2u**	44

Table 2 (*Contd.*)



Entry	(*Z*)-enyne	RYYR	Product	Yield A% (B%)[a,b]
22	**1h**		 **2v**	43
23	**1h**	*n*-BuSe)$_2$	 **2w**	64
24	 **1i**		 **2x**	45
25	 **1j**		 **2y**	46 (Trace)
26	**1j**		 **2z**	43
27	**1j**		 **2aa**	51
28	 **1l**		 **2ab**	37

[a] Reaction conditions A: enyne (0.25 mmol), diorganoyl dichalcogenide (0.55 equiv), $FeCl_3$ (1 equiv) in CH_2Cl_2 (3 mL) under reflux for 2 h. Reaction conditions B: enyne (0.25 mmol), diorganoyl dichalcogenide (0.55 equiv), $FeCl_3$ (0.2 equiv) in DMSO (3 mL) at 110 °C under air atmosphere for 12 h. [b] Yields of isolated products.

Results and discussion

The structure–activity relationship studies were planned using 3-(4-fluorophenylselenyl)-2,5-diphenylselenophene as a prototype molecule and a series of chemical alterations were performed. In an attempt to investigate the potential antidepressant-like action of a series of 3-chalcogen selenophenes prepared, the mouse forced-swimming test (FST) was carried out. The FST is a well-established screening paradigm for antidepressants.[34] Immobility is thought to reflect either a failure to persist in escape directed behavior after persistent stress or the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli.[35] This immobility, referred to as behavioral despair in animals, is claimed to reproduce a condition similar to human depression and is reduced by several agents therapeutically effective in this disorder.[36]

As previously demonstrated by Gay *et al.*,[3] selenophene **2c**, administered by i.g. route at the dose of 50 mg kg^{-1}, reduced significantly (by around 60%) the total immobility time of mice in the FST (p <0.001). The positive control, paroxetine, at the dose of 16 mg kg^{-1}, given 45 min earlier by i.p. route, decreased the immobility time in the FST by around 68% (p < 0.001)

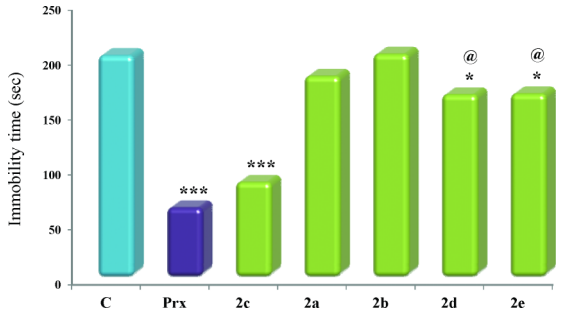


Fig. 1 Effect of an acute administration of selenophenes **2a**, **2b**, **2c**, **2d** and **2e** on the immobility period in the mouse FST. Selenophenes were intragastrically administered at 30 min before FST. Values represent means of total immobility time for six mice in each group. Standard deviation (SD) of all groups represents <10% of means. *** P <0.001 and * P <0.01 when compared to the control group. @ P <0.05 when compared to the compound **2c**-treated group. C means control, a group of mice treated with canola oil. Prx means paroxetine, mice were administered with paroxetine 16 mg kg^{-1}, i.p., 45 min before FST.

(Fig. 1). Compound **2c** has a fluorophenyl portion and at the same dose, route and pretreatment time has been reported to interact with the serotonergic system, particularly by its inhibitory effect on 5-HT uptake in synaptosomes of mouse brain.[3] In fact, the importance of fluorine in medicinal chemistry is well recognized. Fluorine has played a particularly important and historical role in the development of biologically active agents, as antimicrobial, anticancer, anticoagulant, cardioprotective, anti-inflammatory, hypoglycemic, antipsychotic and antidepressant drugs.[37] The presence of 4-fluorophenyl group appears to be essential for optimum potency of neuroleptic agents, spiroperidol and haloperidol.[38] Further, the fluorophenyl group is also found in the structure of other drugs that, like selenophene **2c**, inhibit 5-HT reuptake, such as paroxetine, citalopram and escitalopram. Thus, the structural similarity between compound **2c** and these SSRIs raises the hypothesis that the antidepressant-like mechanism of compound **2c** could be related to the presence of the fluorophenyl portion.

In order to confirm the importance of the fluorophenyl portion to the antidepressant-like action of selenophenes, some examples of selenophenes containing substituents at the phenyl group bonded to the selenium atom were investigated in the mouse FST. The antidepressant-like action of selenophenes **2a** (without a substituent), **2b** (with a methyl substituent), **2d** (with a *p*-chloro substituent), and **2e** (with a *m*-CF_3 substituent) was investigated (Fig. 1). Compounds **2a** and **2b** did not elicit antidepressant-like action in the mouse FST. By contrast, compounds **2d** and **2e** showed a significant effect in reducing the total immobility period (by around 17%), exerting an antidepressant-like action. Moreover, selenophenes **2d** and **2e** were significantly less effective as antidepressant-like agents than compound **2c** (note the immobility time elicited by **2c**, 96 s, compared to **2d**, 166 s, and **2e**, 167 s) (Fig. 1).

Fluorine is the second smallest element with a size approximately 20% larger than the smallest element, hydrogen, and a stepwise substitution of a hydrogen by fluorine, chloro or trifluoromethyl group gradually increases bulkiness.[39] Based on the fact that the fluorophenyl portion could represent the pharmacophoric group of selenophene **2c** and that chloro and trifluoromethyl groups present higher steric parameters than fluorine, we suppose that steric hindrance promoted by the presence of these groups affects the antidepressant-like action of selenophenes **2d** and **2e**. The results also demonstrated that the antidepressant-like action of selenophenes **2a–2e** significantly depends on the electronic effects. The anti-immobility effects elicited by compounds substituted with *p*-fluorine (**2c**), *p*-chloro (**2d**) and *m*-CF_3 (**2e**) indicate that the presence of electron withdrawing groups affects the pharmacological properties of 3-chalcogen selenophenes.

Despite the fact that steric hindrance and electronic effects can explain structure–activity relationship of the selenophenes tested, we cannot discard the possibility of pharmacokinetic influence on their *in vivo* effects. Chemical modifications performed on selenophene structures could alter their pharmacokinetic properties and then modify their absorption, distribution, metabolism and/or excretion. The absorption and distribution of a drug molecule are controlled by its balance of lipophilicity and hydrophilicity as well as ionization. In fact, the use of fluorine in drug design is an example of a directed strategy to increase lipophilicity, biological half-life and bioabsorption of organic compounds, especially aromatic compounds, improving their therapeutic effectiveness.[37] The fluorophenyl group is slightly more lipophilic than the benzoyl group, but chlorophenyl and trifluoromethyphenyl groups are much more lipophilic.[32] This exceedingly lipophilic property compromises the hydrogen-bonding capability with water molecules and then it hinders the solubility of a drug in intestinal fluid, impairing its absorption. Therefore, the different absorptive properties of the selenophenes studied could also explain the higher effectiveness of compound **2c** than **2d** and **2e**. In addition, the strategic incorporation of fluorine into organic molecules has been also widely used to prevent deactivation of biologically active substances *in vivo* increasing their biological half-life. According to Begue and Bonnet-Delpon (2006)[39] the replacement of a specific C–H bond with a C–F bond can effectively block metabolic processes, which can also help us to explain the more potent antidepressant-like action showed by selenophene **2c** in mice.

The logical next step in our investigation was to further clarify whether substitutions at the 2 and 5-positions of the selenophene ring could alter the antidepressant-like activity of the selenophene. In order to answer this question compounds **2m**, **2o** and **2s** were challenged in the mouse FST (Fig. 2). Interestingly, selenophene **2m** did not produce an anti-immobility effect in mice, suggesting that the presence of the fluorophenyl group bonded to the selenophene ring did not confer an antidepressant-like activity (Fig. 2).

Compound **2s** did not decrease the immobility time of mouse in the FST (Fig. 2). Therefore, the lack of an anti-immobility effect shown by compound **2s** leads to the assumption that the phenyl group at the 2-position of selenophene ring is necessary for the antidepressant-like action of this class of compounds (Fig. 2). In addition, selenophene **2o** decreased significantly the immobility time by around 52% (Fig. 2). This result suggests that the removal of the phenyl group attached to the 5-position of selenophene ring does not alter its antidepressant-like action. Thereby we postulate that, in addition to the fluorophenyl portion directly bonded to the selenium atom at the 3-position of selenophene, the presence of a phenyl group bonded at the 2-position of the selenophene

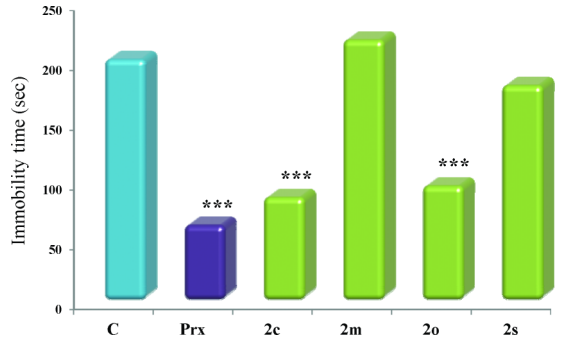


Fig. 2 Effect of an acute administration of selenophenes **2m**, **2o** and **2s** as compared to **2c** on the immobility period in the mouse FST. Selenophenes were intragastrically administered 30 min before FST. Values represent means of total immobility time for six mice in each group. Standard deviation (SD) of all groups represents <10% of means. *** P <0.001 when compared to the control group. C means control, a group of mice treated with canola oil. Prx means paroxetine, mice were administered with paroxetine 16 mg kg^{-1}, i.p., 45 min before FST.

ring is essential for the antidepressant-like action of selenophene in mice.

To further prove the real influence of the selenium group at the 3-position of selenophene in the antidepressant-like activity, we investigated the effect of two groups: a bromine (**3a**) and a secondary alcohol group (**4a**, **4b** and **4c**) in the mouse FST. Compounds **3a**, **4a**, **4b** and **4c** did not reduce the immobility time in the mouse FST (Fig. 3). As a result, the lack of anti-immobility effect of these compounds further proves that the organoselenium group at the 3-position of selenophene is essential for the antidepressant-like activity of selenophenes.

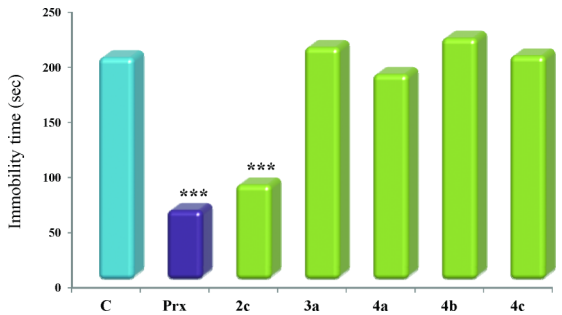


Fig. 3 Effect of an acute administration of selenophenes **3a**, **4a**, **4b** and **4c** as compared to **2c** on the immobility period in the mouse FST. Selenophenes were intragastrically administered 30 min before FST. Values represent means of total immobility time for six mice in each group. Standard deviation (SD) of all groups represents <10% of means. *** P <0.001 when compared to the control group. C means control, a group of mice treated with canola oil. Prx means paroxetine, mice were administered with paroxetine 16 mg kg^{-1}, i.p., 45 min before FST.

Conclusion

In summary, we have demonstrated the $FeCl_3$–diorganoyl dichalcogenide-mediated cyclization of (*Z*)-enynes giving 3-organochalcogen chalcogenophenes in good yields under mild conditions. In addition, 3-chalcogen selenophenes were treated under selenium/lithium exchange conditions with *n*-BuLi and trapping of the lithium intermediates with aldehydes provided the corresponding secondary alcohols, and refluxing the selenophene **2a** with an excess of bromine in a $CHCl_3$ solution gave the product bromide derivatives in good yields. Selenophenes **2c**, **2d**, **2e** and **2o** showed a significant antidepressant-like action when investigated in the mouse FST. The structure–activity relationship studies clearly show that the phenyl group at the 2-position and an organoselenium group at the 3-position of the selenophene ring are essential for the antidepressant-like activity of selenophenes. A close inspection of the results also revealed that the fluorophenyl portion in the organoselenium group is fundamental for the antidepressant-like action of this class of organochalcogen. The results of this study indicate that compounds **2c** and **2o** are promising novel selenophene compounds with potential for the treatment of human depression. Our research group has been engaged in targeting the exact mechanism by which these selenophenes play their antidepressant-like action.

Experimental section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz on a DPX-200 NMR spectrometer or at 400 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz on a DPX-200 NMR spectrometer or at 100 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. All synthesized and tested compounds were obtained in purity superior to 98% determined by combustion analysis, HPLC and gas chromatography.

General procedure for iron-promoted cyclization of *Z*-chalcogenoenynes and diorganoyl dichalcogenides (Condition A)

To a Schlenck tube, under argon, containing a mixture of $FeCl_3$ (0.25 mmol) in dry CH_2Cl_2 (2 mL) was added the appropriate diorganoyl dichalcogenide (0.55 equiv). The resulting solution was stirred for 15 min at room temperature. After this, *Z*-chalcogenoenyne (0.25 mmol) in CH_2Cl_2 (1 mL) was added and resulting solution was stirred under reflux for 3 h. After that the solution was cooled to room temperature, diluted with dichloromethane (10 mL), and washed with saturated aq NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane as the eluent.

General procedure for iron-catalyzed cyclization of *Z*-chalcogenoenynes and diorganoyl dichalcogenides (Condition B)

To a solution of DMSO (2 mL), $FeCl_3$ (20 mol%), under air atmosphere, was added the appropriate diorganoyl dichalcogenide (0.55 equiv). The resulting solution was stirred for 15 min at room temperature. After that *Z*-chalcogenoenyne (0.25 mmol) in DMSO (1 mL) was added and resulting solution was stirred under reflux for 12 h. After that the solution was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with saturated aq NH_4Cl (3 × 10 mL). The organic phase was separated, dried over

$MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane as the eluent.

2,5-Diphenyl-3-(butylseleno)selenophene (2j)

Yield Condition A: 0.077 g (74%). Yield Condition B: 0.070 g (67%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.60–7.51 (m, 5 H), 7.44–7.24 (m, 6H), 2.79 (t, J = 7.7 Hz, 2H), 1.59 (quint, J = 7.7 Hz, 2H), 1.30 (sex, J = 7.7 Hz, 2H), 0.83 (t, J = 7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.95, 146.99, 136.26, 135.71, 131.44, 129.34, 128.91, 128.22, 127.79, 127.77, 126.03, 122.63, 32.15, 28.56, 22.71, 13.46. MS (EI, 70 eV) m/z (relative intensity): 419 (58), 361 (19), 283 (100), 202 (81), 126 (6), 102 (7), 89 (8). Anal. (%) Calcd for $C_{20}H_{20}Se_2$: C 57.43; H 4.82. Found: C 57.62, H 4.89.

2,5-Bis(4-fluorophenyl)-3-(phenylseleno)selenophene (2m)

Yield Condition A: 0.092 g (78%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.53–7.21 (m, 10H), 7.11–7.00 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.66 (d, J = 248.09 Hz), 162.62 (d, J = 248.09 Hz), 148.27, 132.45, 132.36, 131,90 (d, J = 3.659 Hz), 131.78 (d, J = 3.659 Hz), 132.45, 132.43, 132.36, 131.07 (d, J = 8.05 Hz), 129.31, 127.75 (d, J = 8.05 Hz), 126.80, 122.58, 115.84 (d, J = 21.95 Hz), 115.36 (d, J = 21.95 Hz). MS (EI, 70 eV) m/z (relative intensity): 476 (67), 396 (68), 316 (26), 238 (100), 220 (14), 187 (11), 107 (15), 77 (6). HRMS calcd for $C_{22}H_{14}F_2Se_2$: 475,9394. Found: 475.9381.

2-Phenyl-3-(4-fluorophenylseleno)selenophene (2o)

Yield Condition A: 0.066 g (66%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.89 (d, J = 5.73 Hz, 1H), 7.52–7.45 (m, 2H), 7.43–7.27 (m, 5H), 6.92 (t, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.95 (d, J = 246.18 Hz), 149.09, 136.31, 135, 86 (d, J = 8.08 Hz), 131.36, 130.11, 129.38, 128.32, 128.05, 126.55 (d, J = 3.65 Hz), 121.98, 116. 32 (d, J = 21.96 Hz). MS (EI, 70 eV) m/z (relative intensity): 382 (58), 302 (63), 287 (6), 221 (32), 206 (13), 150 (10), 126 (45), 115 (100), 89 (12), 77 (10), 51 (5). Anal. (%) Calcd for $C_{16}H_{11}FSe_2$: C 50.55; H 2.92. Found: C 50.71, H 2.98.

2,5-Dibutyl-3-(butylseleno)selenophene (2w)

Yield Condition A: 0.060 g (64%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.81 (s, 1H), 2.92 (t, J = 7.7 Hz, 2H), 2.83–2.69 (m, 4H), 1.72–1.53 (m, 6H), 0.97–0.85 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.71, 149.08, 131.87, 120.47, 35.14, 34.34, 33.06, 32.50, 29.92, 28.45, 22.80, 22.61, 22.13, 13.90, 13.79, 13.55. MS (EI, 70 eV) m/z (relative intensity): 380 (92), 337 (53), 323 (66), 381 (100), 243 (92), 201 (57), 135 (33), 91 (81), 55 (41). HRMS calcd for $C_{16}H_{28}Se_2$: 380.0521. Found: 380.0533.

Animals

The behavioral experiments were conducted using male adult Swiss mice (25–30 g) maintained at 22–25 °C with free access to water and food, under a 12 : 12 h light/dark cycle, with lights on at 7:00 a.m. All manipulations were carried out between 08:00 a.m. and 04:00 p.m and the experiments were performed according to a randomized schedule. All tests were performed on separate groups of animals and each animal was used only once in each test. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Maria, Brazil (# 124/2010). The procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animals' suffering and to reduce the number of animals used in the experiments.

Drugs

For behavioral tests, selenophenes **2a**, **2b**, **2c**, **2d**, **2e**, **2m**, **2o**, **2s**, **3a**, **4a**, **4b** and **4c** were dissolved in canola oil and administered intragastrically (i.g.). A single dose of 50 mg kg^{-1} was used for all compounds for comparison purposes. Paroxetine, a positive control, was dissolved in saline and administered intraperitoneally (i.p.) at the dose of 16 mg kg^{-1}. Mice received selenophenes and paroxetine in a constant volume of 10 ml kg^{-1} of body weight. Appropriate vehicle-treated groups were also simultaneously assessed. The dose of 50 mg kg^{-1} and the pretreatment time of 30 min were chosen based on a previously published study that established the time and the dose at which compound **2c** reached its maximum anti-immobility effect.[11]

Forced swimming test (FST)

The FST, as originally described by Porsolt (1977),[34a,b] is the most widely used pharmacological assay for assessing antidepressant activity. In this test, mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 ± 1 °C. The total duration of immobility was recorded during the last 4 min of the 6-min period after 30 min of selenophenes (50 mg kg^{-1}, i.g.) or canola oil (10 ml kg^{-1}, i.g.) administration. Paroxetine, administered at the dose of 16 mg kg^{-1} (i.p.), 45 min before FST, was used as a positive control. Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like action.[35]

Statistical analysis

The experimental results are presented as the mean ± S.E.M. The non-paired t-test was considered appropriate to compare the immobility times between control groups and selenophene-treated groups. These analyses were performed using GraphPad Prism version 5, and a significance level of 0.05 was chosen.

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